EFFECT OF PUNCH CONFIGURATION ON DRUG RELEASE FROM HYDROPHILIC MATRIX TABLETS

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I. Abstract:

Hydrophilic matrix tablets present a convenient method for oral modified drug delivery. The performance of such dosage forms is affected by multiple factors, amongst which the influence of tablet shape and structural properties have been partially investigated in previous literature. This work focused on investigating the influence of changing tablet properties on the in-vitro behaviour of hydrophilic matrix tablets, in particular, the influence of tablet face curvature on the hydration and drug release behaviour of round and elongated Xanthan Gum tablets containing the two model drugs Orphenadrine Citrate and Orphenadrine Hydrochloride. The influences of tablet overall porosity and of the formulation used on tablet behaviour were also investigated, in addition to the investigation of any interactions between the influences of tablet and formulation variables.

Initially the properties of the powders incorporated into the various formulations used were characterised. The physical properties of the dry tablets were then investigated in terms of tablet tensile strength and

structural properties. The hydration behaviour of the various tablets was investigated quantitatively using live in-situ swelling studies and qualitatively using rheological and calorimetric methods. Finally the process of drug and polymer dissolution from the tablets was investigated.

The results of the work indicated that tablet face curvature had a significant influence on the physical properties of the dry tablets as well as on the hydration and dissolution patterns associated with the hydrated tablets. The influence of tablet overall porosity was profound on the properties of the dry tablets but became rather minor upon tablet hydration. The type of formulation had a major influence on the properties of dry tablets. Moreover, ionic interactions between the two drugs and Xanthan Gum had a significant influence on the properties of hydrated tablets. Thus, tablet face curvature, porosity of the tablets and physico-chemical properties of the drugs need to be considered when formulating a hydrophilic matrix tablet.

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VI. List of abbreviations:

HPMC	Hydroxypropyl Methylcellulose.
HEC	Hydroxyethyl Cellulose.
HPC	Hydroxypropyl Cellulose.
MCC	Microcrystalline Cellulose.
SLS	Sodium Lauryl Sulfate.
CTAB	Cetyl Trimethyl Ammonium Bromide.
HCl	Hydrochloride.
SEM	Scanning electron microscopy.
CLSM	Confocal laser scanning microscopy.
NMR	Nuclear magnetic resonance.
MRI	Magnetic resonance imaging.
Q	The amount of drug released at time t per unit area of the planar matrix system
A	The initial amount of drug in a planar matrix system.
C_s	The solubility of the drug in the penetrating medium.
D	The diffusivity or diffusion constant of the drug in the matrix (polymer).
τ	The tortuosity factor of a matrix system.
ε	The porosity of a matrix system.
K	Dissolution rate constant of the drug.
M_t	The amount of drug released at time t.
M_∞	The total amount of drug present in the device
n	The diffusional exponent of drug release.
k1	Constants related to the diffusion process.
K2	Constants related to the relaxation process.
m	The Fickian diffusion exponent for a controlled release

	device of any shape.
V_t	The volume of the tablet.
r	The radius of a round tablet.
t	The height of a round tablet.
V_c	The volume of the cap of a round tablet.
h	The height of the cap of a round tablet.
W	The height of cylindrical part of a round tablet.
R	The radius of tablet curvature for a round tablet.
b	The width of an elongated tablet.
l_t	The length of an elongated tablet.
d	The thickness of rectangular section of an elongated tablet.
V_{ce}	The volume of curved segment of an elongated tablet.
a	The height of curved segment of an elongated tablet.
ρ_{mix}	The apparent density of the powder mixture.
ρ_{powder}	The apparent density of the individual powders.
X_{powder}	The percentage fraction of each powder in the powder mix.
ρ_{tab}	The density of the tablet.
ε_t	The porosity of the tablet.
W_{tab}	The weight of the tablet.
V_{tab}	The volume of the tablet.
σ_t	The diametral tensile strength of round tablets.
P	The breaking load of a round tablet.
D	The diameter of a round tablet.
σ_f	The flextural tensile strength of an elongated tablet
F	The breaking load of an elongated tablet.
l	The distance between the two lower rolls of a physical testing instrument.

d	The thickness of an elongated tablet.
a	The height of the curved segment of an elongated tablet.
A	The area of the curved segment of an elongated tablet.
SI_a	The axial swelling index of a round tablet.
$heigh_t$	The height of a round tablet at time *t*.
$height_0$	The height of a round tablet at time *0.*
SI_r	The radial swelling index of a round tablet.
$diameter_t$	The diameters of a round tablet at time *t.*
$diameter_0$	The diameters of a round tablet at time *0.*
SI_h	The height swelling index of an elongated tablet.
$heigh_{t\text{-}mean}$	The mean value of an elongated tablet height at time *t.*
$height_{0\text{-}mean}$	The mean value of an elongated tablet height at time *0.*
SI_w	The width swelling index of an elongated tablet.
$width_{t\text{-}mean}$	The mean value of an elongated tablet width at time *t.*
$width_{0\text{-}mean}$	The mean value of an elongated tablet width at time *0.*
SI_l	The length swelling index of an elongated tablet.
$length_t$	The length of an elongated tablet at time *t*.
$length_0$	The length of an elongated tablet at time *0*.
W_{mix}	The weight of the powder mixture used in gel preparation.
C_g	The concentration of the gel.
W_w	The weight of powder used in gel preparatiob.
X_p	The percentage fraction of the polymer in the powder mixture used for gel preparation.
Pa	Pascal.
Hz	Hertz.
UV	Ultraviolet.
λ	Wavelength.
rpm	Rotation per minute.

kV	Kilovolt.
magn.	Magnification.
APD	Apparent powder density.
DSC	Differential scanning calorimetry.
ANOVA	Analysis of variance.
p	Significance.
df	Degrees of freedom.
MANOVA	Multivariate analysis of variance.
G’	Elastic modulus.
G”	Viscous modulus.
LVR	Linear viscoelastic region.
δ	Phase angle
η	Apparent viscosity.
$\dot{\gamma}$	Shear rate.
σ	Shear stress.
γ	Strain.
η_i	Instantaneous viscosity.
R^2	Correlation coefficient.

CHAPTER ONE

1. Introduction:

1.1. Hydrophilic matrix systems:

1.1.1. General features:

Matrix systems containing hydrophilic “swellable” polymers continue to form an important part of modified release dosage forms. They are referred to using various names, including hydrocolloid matrices (Mockel and Lippold 1993), hydrogel matrices (Lee 1985), and swelling-controlled release systems (Korsmeyer and Peppas 1983). However the most often used terms are hydrophilic matrix tablets (Ford 1994), and swellable matrix tablets (Colombo et al 2000). Such devices have been used for many routes of drug delivery, such as buccal, ocular, rectal, and vaginal. However, they are mainly used in the formulation of oral solid dosage forms, and they present a variety of advantages over other delivery systems. Most importantly the low cost of carrier polymers, availability of equipment needed to produce them, and ease of formulation and manufacture (Melia 1991, Collett and Moreton 2002).

Melia (1991) also listed a few advantages related to the type of carrier polymers used in these systems including the availability of the polysaccharides used as carriers, which permits the manipulation of the formulation to achieve individual needs. Moreover, the matrices produced are bio-erodible, i.e. they erode as they descend through the GI tract and thus avoid any accumulation of exhausted systems ("ghosts") inside the body, and this is a major advantage over inert matrices that remain undissolved in the GI tract. One disadvantage associated with the naturally occurring hydrophilic polymers used in the production of such systems is the batch to batch variability in polymer properties.

1.1.2. Mechanism of action:

1.1.2.1. Hydration:

Hydrophilic matrix systems are hydration activated systems; i.e. the action of such systems and hence drug release from them depends upon the interaction of the polymer molecules with the hydration medium, causing a cascade of changes that lead at the end to the release of the drug substance into the surrounding medium.

Upon contact with an aqueous medium, water penetration into the dosage form is initiated, causing the polymer molecules on the periphery to hydrate. Furthermore, water decreases the glass-transition temperature of the polymer which undergoes a process of relaxation and swelling forming a rubbery gelatinous layer that retards further water

penetration, and impedes the rate of drug release into the surrounding medium. With further hydration and swelling of polymer molecules on the surface of the gel layer, they could reach a certain concentration called the polymer disentanglement concentration at which individual polymer molecules undergo a process of disentanglement causing their slow erosion from the periphery of the matrix and their subsequent transport to the bulk medium. These two mechanisms lead to the characteristic cycle of the gel layer formation. At the beginning of water penetration into the matrix, this causes the relaxation and swelling of the polymer molecules on the surface of the matrix which leads to the formation and thickening of the gel layer. Continuous hydration of the polymer leads to the disentanglement of fully hydrated polymer molecules from the surface of the polymer. When the two processes of polymer swelling and erosion are synchronised, the thickness of the gel layer remains constant for a while. With further hydration, polymer erosion starts taking over leading to the thinning of the gel layer (Colombo et al 1996, 1999, 2000).

Several studies have examined the ingress of water into hydrophilic matrix systems and the formation of the gel layer. They have shown the formation of a multilayered system inside the dosage form as a result of water penetration, and the presence of three fronts moving inside the dosage form, starting from an erosion front on the interface with the surrounding medium, then a diffusion front and finally a swelling front (Colombo et al 1999, Ferrero-Rodriguez et al 2000).

The erosion front lies on the interface between the surrounding medium and the dosage form, and represents the boundary at which polymer and drug molecules are released into the surrounding medium. The diffusion front represents the boundary between the dissolved and undisolved drug molecules in the gel layer, and this front is more apparent with less soluble drug substances where the movement of the solvent into the dosage form is not matched by the dissolution of the drug molecules. The swelling front however represents the boundary between the gel layer region containing the hydrated polymer, and the dry core of the dosage form.

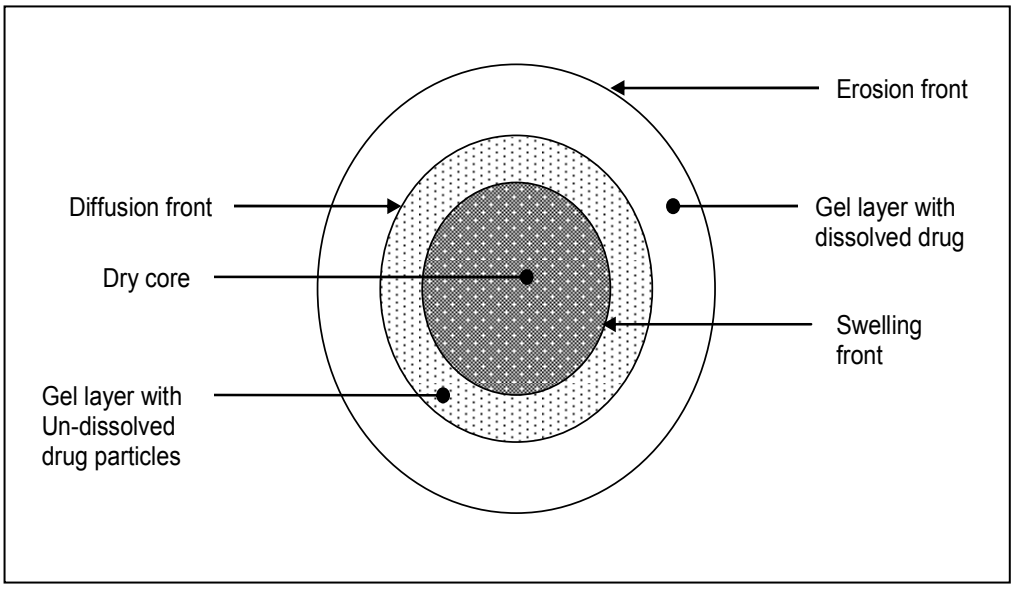

Figure 1.1. Schematic representation of the various layers and fronts formed within a hydrating hydrophilic matrix dosage form.

The movement of the previous three fronts and the resulting gel layer they form inside the dosage form have been shown to be a principle factor that governs the release of the drug substance from a hydrophilic matrix system (Colombo et al 1999, Ferrero Rodriguez et al 2000).

1.1.2.2. Drug release:

The type of the gel layer formed, more precisely the thickness and the physical and mechanical properties of the gel layer are the principle factors affecting drug release from hydrophilic matrix systems. Drug transport is governed by a balanced mechanism arising from the two processes that control the gel layer formation. On one side there is the hydration and swelling of the polymer forming the gel layer that acts as a physical barrier hindering the free movement of the drug molecules and forcing them to diffuse through it, and on the other side there is the disentanglement of the polymer molecules into the surrounding medium which reduces the thickness of the gel layer and at the same time causes the drug molecules if still un-dissolved to erode into the surrounding medium. The effect of each of the previous processes differs with the differing solubility of the drug. Drugs with sufficient solubility depend mainly on diffusion through the gel layer and hence are affected by the rate of drug dissolution, and by polymer erosion which governs the gel layer thickness through which drug molecules have to diffuse. Drugs with insufficient solubility would be released mainly by the erosion of their

particles into the surrounding medium with eroding polymer molecules (Huber et al 1966, Colombo 1996).

1.1.3. Polymers used in the formulation of hydrophilic matrix systems:

Many polymers of varying properties have been utilised in the preparation of hydrophilic matrix dosage forms, all of which share a common feature of being hydrophilic polysaccharides. However, such polymers differ a lot in their physicochemical properties, giving rise to matrix systems with varying properties, and with different patterns of hydration. The following are some of the major types of hydrophilic polymers successfully employed in the preparation of hydrophilic matrix systems:

1.1.3.1. Natural Polymers:

1.1.3.1.1. Xanthan gum:

Xanthan gum is a microbial extra-cellular anionic polysaccharide produced by various strains of the bacteria *Xanthomonas Camperisis* (Lachke 2004). This gum has wide applications in the pharmaceutical industry due to its thickening and emulsifying effects. It was also successfully incorporated into oral modified release solid dosage forms like TIMERx® in which the advantageous synergistic gellation between Xanthan Gum and Locust bean gum were exploited (Anand et al 1991, 1992a, 1992b).

Several workers evaluated the use of xanthan gum in the formulation of modified drug delivery systems (Fu Lu et al 1991, Dhopenshwarker and Zats 1993, Ntawulkulilyayo et al 1996, Billa et al 2000, Andreopoulos et al 2001). Several studies reported the ability to obtain constant “zero-order” drug release using Xanthan Gum, especially at higher gum contents (Sujja-Areevath 1996, Talukdar et al 1996b, Munday and Cox 2000).

Comparing the efficiency of Xanthan Gum in modifying drug release with that of other polymers has also been addressed. When compared with HPMC, Xanthan Gum showed higher drug sustaining ability, in addition to other advantages such as the lack of burst effect and the possibility of obtaining zero order drug release patterns (Talukdar et al 1996b). The more rapid drug release from HPMC matrices was attributed to higher drug diffusion in the gel layer of HPMC matrices compared to Xanthan Gum matrices (Talukdar et al 1997). More insight into this difference could be accomplished by observing earlier results reported by the same group; they compared the rheological properties of Xanthan Gum and HPMC solution at concentrations of 4 and 7% which are similar to polymer concentrations in the outer gel layer. They found that the behaviour of Xanthan Gum solutions at such concentrations is comparable to a gel and that the dynamic behaviour of Xanthan Gum is only weakly affected by the frequency of the shear it is subjected to. HPMC solutions however were not able to form a gel and behaved like normal polymer solutions; the dynamic behaviour of HPMC solutions was more prone to variation in the rate of shear (Talukdar et al 1996a).

Drug release from mini-matrices containing Xanthan Gum and other gums was evaluated and it was shown that the ability of Xanthan Gum to sustain drug release was higher than other natural gums (Sujja-Areevath et al 1996). Further investigation revealed that Xanthan Gum had the highest swelling ability that was also accompanied by a moderate erosion rate. Other natural Gum like Karaya Gum however had a moderate swellability, but also a low erosion rate (Sujja-Areevath et al 1998). However, conflicting results were noted by Munday and Cox (2000) who reported that Xanthan Gum matrices exhibited a higher degree of swelling and less degree of erosion than Karaya Gum matrices. One possible factor influencing such a difference in results may lie in the nature of dosage forms used in both studies; both studies report using USP basket method for erosion studies. However, Sujja-Areevath et al (1996, 1998) used mini-matrices of smaller diameter than the ones used by Munday and Cox (2000). The small size of the mini-matrices could have caused faster hydration especially when the polymer used has enhanced swelling properties. This factor when coupled with the attrition effect of the basket could lead to more erosion of the highly hydrated matrices.

One major determinant of the swelling ability of Xanthan Gum and hence its efficiency in modifying drug delivery is the ionic strength of the hydration environment. Talukdar et al (1993) reported rapid disintegration of tablets containing small amounts of Xanthan Gum when placed in a NaCl solution of 0.1 M or more leading to rapid drug release, and this was

slightly overcome by increasing the polymer content and inclusion of binders (Talukdar et al 1993). With further investigation they noted that the swelling of Xanthan Gum tablets had a reciprocal relationship with the ionic strength of the dissolution medium and that was not affected by the type of ions present (Talukdar et al 1995). This phenomenon had a more pronounced effect on the release of water soluble drugs that are released mainly by diffusion; the release of such agents was enhanced in the presence of salt into the dissolution medium (Talukdar et al 1997). Dhopenshwarker and Zats (1993) found that the pH of the hydration medium on drug release from Xanthan Gum tablets is only apparent with the initial phase of drug release which was faster in simulated gastric fluid than simulated intestinal fluid. However, no apparent difference was reported for drug release in later stages and this was attributed to the faster erosion at the surface of the tablets before sufficient polymer hydration and swelling has taken place.

1.1.3.1.2. Galactomannans:

Guar gum is a poly-galactomannan gum in which the structural chain is made up of D-mannose units with 1-4 linkages (Lawrence 1973). The use of Guar Gum in the formulation of hydrophilic matrix based systems is mentioned in the literature; Khullar et al prepared matrix tablets containing Guar Gum with Theophylline anhydrous as a model drug. They noted the ability of guar gum in sustaining drug release for a long period of time which was mainly through diffusion. This was attributed to

the steady swelling of the gum (Khullar et al 1998). The ability of Guar gum to provide sustained release of Diltiazem, whether used alone or mixed with smaller amounts of other hydrophilic polymers, was comparable to that of commercial slow release Diltiazem tablets, with little effect caused by the change of gum batch or dissolution hydrodynamics (Altaf et al 1998).

Krishnaiah et al studied the use of Guar Gum matrix tablets in sustaining the release of the highly water soluble model drug Metoprolol tartrate. They reported that normal matrix tablets failed to sustain the release of the drug. However, a developed three layered Guar Gum matrix tablet with two drug free layers on the outer part provided sustained drug release which was not affected by storage (Krishnaiah et al 2001).

Locust Bean Gum is another Galactomannan obtained from the fruit seeds of the Locust or Carob tree, (Lawrence 1973). Uner et al (2004) investigated the release of Theophylline from matrix tablets prepared with honey locust bean gum. They showed that there was no difference in drug release between commercial tablets and those prepared using honey Locust Bean Gum which maintained a zero-order release process. When compared with other gums in the preparation of mini-matrices, locust been gum showed an ability in sustaining drug release similar to Xanthan and Karaya gums (Sujja-Areevath et al 1996). However it had a higher rate of erosion compared to the other gums (Sujja-Areevath et al 1998).

1.1.3.1.3. Chitosan:

Chitosan is a de-acetylation derivative of chitin which is a natural polymer found in crab and shrimp shells. (Bhardwaj et al 2000). Several works have studied the combination of Chitosan with other hydrophilic polymers. Hasan et al (2003) demonstrated the ability of a combined polymer mixture of Chitosan with Alginate in sustaining the release of the drug Metoclopramide both in vitro and in vivo. When comparing different polymer mixtures, a Chitosan Alginate mixture was better in sustaining the release of the drug Diltiazem Hydrochloride than a Chitosan Carrageenan mixture (Tapia et al 2004).

The ability of Chitosan to form various salts has also been examined. An acetate salt derivative of Chitosan prepared by spray drying demonstrated its ability to sustain the release of Theophyline when used as a binder in tablets at a concentration of 3 % w/w (Nunthaid et al 2004).

1.1.3.1.4. Sodium Alginate:

Alginates are hydrophilic polymers obtained from Alginic Acid which is a phyco-colloid found in brown algae (Lawrence 1973). Guinchedi et al (2000) studied the ability of alginate in retarding the release of Ketoprofen. They found that matrices prepared with alginate alone, or in combination with HPMC were able to sustain the release of the drug Ketoprofen. However, alginate based systems are highly affected by crosslinking agents. Incorporation of calcium gluconate into the matrices

prepared by Guinchedi et al (2000) reduced the ability of the matrices to retard drug release. This was attributed to the cross-linking of alginate in the presence of the calcium ions and the effect this may have on the gel layer. Moreover, the soluble calcium ions have the ability to act as a channelling agent in the gel layer and thus increase the porosity of the matrix.

When compared with Carbopol which is a highly cross linked polymer, the linear alginate showed less ability in sustaining the release of the drug Furosemide. This was explained by the different drug release behaviour of the two polymers in aqueous media; drug release from alginate was mainly through polymer erosion and polymer dissolution, whereas Carbopol had a combined diffusion and polymer relaxation mechanism. (Eftekanis et al 2000)

Opposing effects of the pH of the dissolution medium on the release of water soluble and poorly soluble drugs were reported by Hodsdon et al (1995); a faster release of Chlorpheniramine Maleate, which is a water soluble drug, from alginate matrices occurred in simulated gastric fluid when compared to simulated intestinal fluid. An opposing effect occurred with the poorly soluble drug Hydrochlorthiazide. The previous effect was attributed to the different natures of the gel layer within the different media. Moreover, and as mentioned previously, the change in drug solubility causes a change in the mechanism mainly responsible for its

release. Thus, the change in the properties of the gel layer may have varying effects on drugs with varying solubility.

1.1.3.1.5. Other natural polysaccharides:

Other natural gums and polysaccharides that have been studied as carriers in hydrophilic matrix systems include Karaya Gum (Sujja-Areevath et al 1996, Sujja-Areevath et al 1998, Munday and Cox 2000), Khaya gum (Odeko et al 2004) and tamarind seed polysaccharide (Sumathi et al 2002).

1.1.3.2. Synthetic and modified polymers:

1.1.3.2.1. Cellulose ethers:

Cellulose ethers are widely used in the preparation of hydrophilic matrix dosage forms, and Hydroxypropyl Methylcellulose (HPMC) could be considered the most used matrix former for hydrophilic matrix systems. A large amount of literature dealt with the properties of these polymers and evaluated their ability as hydrophilic matrices.

The different types of cellulose ethers seem to differ in their hydration behaviour upon contact with water, and hence produce matrix systems with differing nature. Ferrero Rodriguez et al (2000) compared the swelling and drug release properties associated with tablets containing different cellulose ethers. They reported several differences between the

various polymer types; for example erosion of the polymer was only high with Hydroxyethyl Cellulose (HEC) which may contribute significantly to drug release, whereas from Methylcellulose matrices drug release was mainly through diffusion. Drug release from matrices containing other cellulose ethers was due to a combination of diffusion and erosion. When comparing Hydroxypropyl Cellulose (HPC) and Hydroxyethyl Cellulose (HEC), Roy et al (2002) found that HEC matrices had a higher degree of swelling and erosion than HPC matrices. The release of the water soluble drug Chloropheniramine Maleate was through diffusion and matrix swelling, whereas for HPC matrices it primarily occurred by diffusion through the gel layer.

Vueba et al (2004) compared the ability of different cellulose ethers in modifying the release of Ketoprofen from matrix tablets. They reported that Methylcellulose and Hydroxypropyl Cellulose were not able to sustain the release of the drug, whereas HPMC was able to do so. When comparing the drug release mechanism and rate, they found that changing the type of the polymer did not affect the mechanism of drug release, but tablets formulated using HPMC gave the highest mean dissolution time for Ketoprofen.

1.1.3.2.2. Other synthetic polymers:

Other synthetic polymers have also been studied and used successfully in the preparation of hydrophilic matrix systems, and they include

Carbomer (Perez-Macros et al 1991), and Polyethylene Oxides (Kim 1998, Maggi et al 2002).

1.1.3.2.3. Modified starches:

Several modified types of starch have been studied as polymers for modified drug release. Retrograde starch was prepared by Wierik et al and it was able to retard the release of various drugs with differing physicochemical properties. Moreover the release of the drugs was not influenced by inclusion of a lubricant or by the activity of α-amylase in the dissolution medium (Te Wierik et al 1996, 1997a, 1997b).

1.1.4. Sources of variation in the behaviour of hydrophilic matrix systems:

The behaviour of hydrophilic matrix systems, and more precisely the process of drug release from such systems, may be easy to evaluate in terms of the underlying structural changes leading to it, and the main mechanisms responsible for drug release. However, the overall drug release process is a much more complicated process in which multiple factors are involved, and play varying roles in modulating the release process in terms of rate and pattern. Certain trends can be associated with some variables, but verifying specific effects for each variable is not a clear cut matter. This could be due to several causes, mainly the varying types of hydrophilic polymers utilised in the formulation of

hydrophilic matrix systems; each having different physicochemical properties from the others, and this, as will be seen shortly, is a major determinant of the degree and nature by which several factors present themselves.

Another cause of such complexity observed in the behaviour of hydrophilic matrix systems arises from the interference of the effects associated with the various factors influencing the processes of polymer hydration and drug release. In the following section, a review of the main variables affecting the behaviour of hydrophilic matrix dosage forms is presented.

1.1.4.1. Formulation ingredients:

1.1.4.1.1. Drug:

The properties of the drug incorporated into hydrophilic matrix systems have a great effect on the behaviour and properties of such systems. Drug properties were reported to have a major effect on matrix swelling and subsequently on the release characteristics of the drug itself.

Drug solubility, as mentioned previously, is a major determinant of the drug release mechanism. It also has an effect on the rate by which the drug is released from the system; the rate of drug release from hydrophilic matrix dosage forms is reported to be higher for drugs with higher aqueous solubility (Lapidus and Lordi 1968, Colombo et al 1995, Yang and Fassihi 1997, Zuleger and Lippold 2001). This is probably due to higher dissolution rate of such drugs upon contact with the penetrating

water which causes the formation of a concentration gradient that enhances the release of the drug out of the system. As the aqueous solubility of the drug decreases, the release rate of the drug is also decreased, (Colombo et al 1995) and this in turn could be due to slow dissolution of the drug which may decrease the driving concentration gradient. With further decrease in drug solubility, the ingress of water into the matrix causes the hydration of the polymer with minimal drug dissolution, causing the suspension of the un-dissolved drug particles in the swollen gel layer which are released into the surrounding medium when polymer erosion is initiated at the erosion front after sufficient polymer hydration takes place. (Kim 1998). Kim studied the effect of drug solubility on drug release from PEO tablets, and he reported slower release of the drug Sulfathiazol compared with other drugs with higher water solubility. The release profile of Sulfathiazole was sigmoidal in shape indicating the presence of a lag time before drug release is enhanced. (Kim 1998). Such results come in accordance with earlier similar results reported by Ford et al (1985b) for the drug Indomethacine using HPMC matrices.

Drug solubility could also lead to variation in the release behavior with time, through affecting the properties of the formed gel layer. Bettini et al (2001) monitored this aspect in HPMC matrices using the three model drugs Buflomedil Pyridoxalphaosphate (BPP), Sodium Diclofenac (DCN) and Nitrofurantion (NTF), with decreasing aqueous solubility respectively. They reported that initial drug release rate was directly related to drug

solubility. However they also report acceleration of the release of DCN after full hydration of the matrix core, and this effect was also observed and more pronounced with NTF which is the least soluble. The change in drug release rate was also coupled with complete disintegration of the matrices containing the less soluble drugs within the dissolution medium, and this was justified by the process of polymer relaxation which caused the dragging of the un-dissolved particles of the less soluble drugs towards the outer region of the gel layer causing a reduction in their diffusion path and at the same time weakening of the gel layer. Ferrero-Rodriguez et al (2000) reported similar results with matrices formed using cellulose ethers.

Another factor exerting an effect on matrix behaviour and drug release is the content of the drug; an increase in the release rate of the drug was reported with the increase in its content (Yang and Fassihi 1997). Similar results were also reported for matrices in which erosion is the predominant factor affecting drug release (Zuleger and Lippold 2001),

The reduction of drug particle size is usually associated with better hydration and dissolution of the drug. However, various trends were reported regarding the effect of drug particle size on drug release patterns from hydrophilic matrix dosage forms. In HPMC matrices containing two model drugs; Propranolol Hydrochloride and Aminophylline, changing the particle size of the model drugs did not have any significant effect on drug release (Ford et al 1985a). In HPMC

matrices containing the drug Oxazepam, increasing the drug particle size while keeping a constant drug to polymer ratio, caused a decrease in its dissolution rate and a shift towards erosion mediated drug release (Tros de llarduya et al 1997). However, when examining this factor in tamarind seed matrices containing caffeine, the increase in drug release was manifested at higher size ranges only and this was attributed to the increase in the porosity of the matrix (Sumathi et al 2003). Such variations in the effect associated with drug particle size could be highly correlated with other factors such as the solubility of the drug itself, or the properties of the hydrophilic polymer utilised in the formulation, and also the properties of other formulation ingredients used.

Fu et al (2003) studied the influence of drug molecular properties; they compared matrix systems containing four water soluble drugs with different molecular volumes and they observed an exponential relationship between the diffusion coefficients of the drugs and their molecular volumes in which drugs with smaller molecular volumes had higher diffusion coefficients.

1.1.4.1.2. Hydrophilic polymer:

The role of the polymer in hydrophilic matrix systems is the formation of the gel layer on the outer surface of the dosage form upon contact with an aqueous medium. As discussed previously, drug release is achieved mainly by diffusion through this gel layer or through erosion of the

hydrated polymer chains at the outer surface of the gel layer. Thus, the properties of the polymer would have a major effect on the structure of the gel layer and subsequently on the process of drug release.

In addition to the type of polymer used in the formulation of hydrophilic matrix systems which have been shown to be a major determinant of the behaviour of such systems, other polymer related variables have been examined.

Decreasing the content of the polymer in the formulation lead to an increase in the drug release rate (Huber et al 1966). However, increasing the polymer content in the matrix system was reported to cause the formation of a thicker gel layer and hence decrease the release rate of water soluble drugs due to increased diffusion pathway (Rekhi et al 1999, Sujja-Areevath et al 1996). The release rate of water insoluble drugs was also reported to decrease with increasing polymer content (Xu and Sunada 1995, Talukdar et al 1998) and this could be explained by the formation of a stronger gel layer that resists erosion.

Several studies reported the significant influence of polymer particle size on the performance of hydrophilic matrix dosage forms; for Xanthan Gum tablets, decreasing the particle size of the polymer resulted in a more sustained release. This was noted with both water soluble and sparingly soluble drugs (Dhopenshwarkar and Zats 1993). Such behaviour could be attributed to the ability of the fine polymer particle to rapidly hydrate,

forming a dense gel layer. On the other hand, coarse fractions of polymer particles resulted in tablet breakage due to their inability to hydrate quickly and form a robust gel layer upon contact with water (Dhopenshwarkar and Zats 1993). Similar results were observed with HPMC tablets in which drug release increased with increasing polymer particle size (Campus-Aldrete and Villafuerte-Robles 1997, Velasco et al 1999).

Another aspect affected by polymer particle size is the very initial phase of drug release; the lag time before drug release is decreased with increasing polymer particle size, and for HPMC matrices no lag time was observed for tablets made with particle size fraction of 150-250 μm, whereas smaller size fractions were able to induce lag time and decrease the burst effect. This was attributed to the fast formation of a gel layer by the rapidly swelling of small particles. (Campus-Aldrete and Villafuerte-Robles 1997)

However, the effect of polymer particle size is highly correlated with the content of the polymer in the formula; its significance is more evident at lower polymer content. Whereas higher polymer content may obscure the effect of particle size (Campus-Aldrete and Villafuerte-Robles 1997, Heng et al 2001). In their study, Heng et al (2001) monitored this phenomenon in HPMC tablets and they reported that when the polymer content was less than 5 %, rapid drug release occurred with all size fractions. At higher polymer content, increased drug release was only apparent with

larger size fractions, and when the polymer content was higher than 20 % the difference between various particle size fractions was less evident.

For polymers having several viscosity grades, as is the case with cellulose ethers and other synthetic polymers like Polyethylene Oxides, this variable could also influence the behaviour of the dosage form into which they are formulated. Studies showed that increasing the viscosity grade of the polymer resulted in an increase in the swelling ability of the polymer molecules and hence decreased drug release rate.(Campus-Aldrete and Villafuerte-Robles 1997, Lee et al; 1999, Katzhendler et al 2000).

1.1.4.1.3. Diluents:

Diluents or fillers are of great importance in the formulation of pharmaceutical tablets due to the multiple advantages they present, starting from increasing the bulk of the formula, modifying the physical properties of the products, and modifying the behaviour of the system in terms of drug release. A substantial amount of literature is available about the effect of different diluents on the behaviour of hydrophilic matrix dosage forms. Two main variables related to such materials are their content and physicochemical nature. Various, and sometimes different, observations have been reported about the effect of such variables on the behaviour of hydrophilic matrix dosage forms, which proves, once more, the complexity of such systems.

Lapidus and Lordi reported an increase in drug dissolution rate when replacing some of the polymer with either soluble or insoluble diluents. They also reported that only at higher diluent content it was possible to differentiate between the effect of water soluble and insoluble ones (Lapidus and Lordi 1966, 1968). In a similar study Ford et al (1987) compared the effect of two diluents on the release of Promethazine HCl from HPMC matrices, namely soluble spray dried lactose and insoluble calcium phosphate, and they observed that replacing part of the polymer with either diluent increased the release rate of the drug, but diffusion remained as the major release mechanism. Moreover, they reported that the difference between the effects of the two diluents was only possible when they are incorporated at high levels, where the effect of spray dried lactose on drug release was more apparent than that of calcium phosphate.

Sujja-Areevath et al (1996) examined the effect of diluent solubility on the release of Diclofenac Sodium from mini-matrices containing different natural gums. They reported that increasing the content of diluent in the formulation resulted in an increase in drug release. Furthermore, drug release pattern shifted more towards erosion than diffusion. They also report that the solubility of the diluent had no significant effect on its effect. Somewhat different results were observed by Cox et al (1999) with Xanthan Gum mini-matrices containing the drug Ibuprofen. They examined the effect of inclusion of various diluents, namely spray dried lactose, microcrystalline cellulose (Avicel®) and Dibasic Calcium

Phosphate Dihydrate (Emcompress®). They reported that the different diluents had different effects on the release of Ibuprofen from the mini-matrices; little difference was seen in drug release between matrices containing spray dried lactose and Emcompress®. However, matrices containing Avicel® exhibited higher drug release and this was attributed to the disintegration enhancing effect of Avicel®, and its influence on the integrity on the matrix and hence on drug release (Cox et al 1999).

The effect of manipulating the polymer to diluent ratio was also examined, and studies were undertaken on Carbopol matrices using lactose, microcrystalline cellulose (MCC) and starch as diluents. Results demonstrated that all diluents enhanced the release of Ibuprofen when incorporated into the matrices. However, the effect of the different diluents varied in its degree; it was highest for starch, which was reported to exert an “explosion effect”, followed by MCC and then lactose. Moreover, increasing the polymer content seemed to have a more drastic effect on the ability of lactose to enhance drug release than that of the two other diluents. (Khan et al 1998, 1999).

Upon comparison of the results reported by various studies, it becomes evident that careful deductions should be made. This is due to the high complexity and correlation between the variables associated with the various diluents, and those associated with other formulation ingredients, such as the solubility of the drug. Moreover, the chemical and

hydrodynamic properties associated with the dissolution environment could have significant effects on matrix hydration and drug dissolution.

1.1.4.1.4. Lubricants and glidants:

Several workers examined the effect of adding various lubricants and glidants on the behaviour of hydrophilic matrix tablets and especially on the process of drug release. Once again, varying results were reported; Sheskey et al (1995) reported that changing the level of Magnesium Stearate from 2.0 % to 0.2% in HPMC 2208 tablets resulted in the production of tablets with higher crushing strength. However, neither the level of the Magnesium Stearate, nor the mixing time had a significant effect on drug release. Similar results were reported by Gupta et al (2001) with Carrageenan matrices. They reported that Magnesium Stearate (0.5%) and Stearic Acid (1%) had no significant effect on the release rate of Theophylline from the tablets. However, Magnesium Stearate at a level of 1% significantly slowed down the release of Theophylline after 4.5 h.

The effect of added lubricants is in turn influenced by the type of polymer used; Lee et al (1999) reported opposing results of the effect of the hydrophobic lubricant, Magnesium Stearate on drug release from tablets containing HPMC of different grades.

From this, and other previously mentioned examples, one could see that the overall formulation rather than a single ingredient is the most significant factor in determining the behaviour of the system.

1.1.4.1.5. Interactions between formulation ingredients:

Potential ionic interactions between the various formulation ingredients, incorporated into hydrophilic as well as other matrix systems, could have a profound effect on the behaviour of such systems and on the dissolution patterns associated with them.

The occurrence of ionic interactions between formulation ingredients has been utilised to manipulate the dissolution of drugs from matrix systems. One of the reported methods depends on the incorporation of ionic surfactants into the formulation. Such surfactants have the ability to interact with oppositely charged drugs and thus retard the process of drug release from the matrix systems. Several workers have focused on this technique and among the surfactants investigated is the anionic surfactant Sodium Lauryl Sulfate (SLS) which was shown to retard the release of the cationic drug Chlorpheniramine Maleate from HPMC matrices (Feely and Davis 1988, Daly et al 1984). The release of the cationic drug Propranolol Hydrochloride from HPMC-Eudragit matrices was also reduced by the addition of the anionic Sodium Lauryl Sulphate, with little effect noted with the addition of the cationic surfactant Cetyl Trimethyl Ammonium Bromide (CTAB). However, incorporation of the cationic CTAB into matrices containing the anionic SLS resulted in faster drug release and this was explained by the interaction of the two oppositely charged surfactants (Nokhodchi et al 2002).

However, some of the most studied interactions are those occurring between ionic polymers and oppositely charged drugs. Such interactions occur between oppositely charged moieties in the structure of the polymer and drug. Such ionic interactions have been studied and attempts have been made to employ their occurrence in modifying the behaviour of matrix systems, more precisely the process of drug release from them. Several ionic polymers have been investigated. The ionic interaction of the anionic Lambda Carrageenen with cationic drugs, mainly Diltiazem Hydrochloride has been examined and compared with other drugs. Moreover, the physicochemical, tabletting, and dissolution properties of the resulting ionic complex between the drug and polymer were examined (Bonferroni et al, 2000a, 2000b, 2004, Aguzzi et al 2002). This polymer was able to modify the release of other cationic drugs from its matrices including Salbutamol Sulfate and Chlorpheniramine Maleate (Bonferoni et al 1993, 1994, 1998).

Other anionic polymers were also shown to be able to retard the release of oppositely charged drugs from their matrices including the retarding influence of Carbopol 934P on the release of Verapamil Hydrochloride through the ionic interaction between the carboxylic groups of the polymer and the tertiary amine groups of the drug (Elkheshen 2001), The cationic polymer Chitosan was also investigated, and it was shown to be able to retard the release of the anionic drug Salicylic Acid when incorporated into its films, through ionic interaction (Puttipipatkhachorn et al 2001).

Takka et al (2001) Showed that changing the type of the anionic polymer incorporated into HPMC matrices had a marked effect on the release of the cationic drug Propranolol Hydrochloride in different dissolution media. In a later study Takka (2003) explained that the previously noted change in drug release behaviour with the change in the type of the anionic polymer resulted from the change in the ionic interaction potential between the drug and the various polymers.

It could thus be seen that the occurrence of ionic interactions between the different materials incorporated into hydrophilic matrix systems, mainly between the ionic polymers and oppositely charged drugs, could actually be regarded as an advantageous point in the development and manipulation of hydrophilic matrix dosage forms.

1.1.4.2. Dosage form:

The shape properties of dosage forms based on hydrophilic matrix systems is one of the major factors affecting the behaviour of such dosage forms. This will be discussed in detail in the next section. However, other variables associated with the nature and with the production of such dosage forms have been examined in terms of their effect on the behaviour of hydrophilic matrix systems.

The compression force used in the production of tablets seems to exert an effect on the initial phase of drug release; Huber et al (1968) reported

that tablets made at various compression force levels did not exhibit significantly different release patterns. HPMC tablets produced at lower compression force values exhibit a more apparent burst effect in terms of drug release. However, after swelling of the tablet, the reported results show no difference between tablets made at different compression force values (Kabanda et al 1994). Similar results were demonstrated by Rizk et al (1994) for matrix tablets formulated with the polymer Scleroglucan. They reported that the compression force which decreases tablet porosity has little effect on drug release.

The storage conditions of matrix tablets seem to have minor effect on their ability to sustain drug release. For Carrageenan tablets, their ability to sustain the release of Theophylline was not affected by three months storage at 37°C and a humidity of 75% (Gupta et al 2001).

1.1.5. Importance of the dosage form shape in matrix systems:

Properties associated with the shape of dosage forms based on hydrophilic matrix systems seem to have a significant effect on the behaviour of such dosage forms, mainly on the process of drug release.

Several studies examined the effect of the geometric shape of the dosage form on drug release. Cobby et al (1974a, 1974b) made some investigation into the effect of varying tablet shape on drug release from insoluble matrices. They developed an equation describing the

dissolution kinetics of drugs from slow release matrix systems based on previous work by Higuchi (1963), taking into account what they called "shape factors" of the tablets (Equation 1.1.).

$$f_t = G_1 K_r t^{1/2} - G_2(K_r t^{1/2})^2 + G_3(K_r t^{1/2})^3 \qquad \textbf{Equation 1.1.}$$

where f_t is the fraction of drug released from the matrix at time t, G_1, G_2, and G_3 are factors based on the shape of the tablet undergoing dissolution, and K_r is a rate constant describing the process of drug release from such tablets, which is calculated using equation 1.2.

$$K_r = \frac{1}{Ar_0}\sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_S)C_S} \qquad \textbf{Equation 1.2.}$$

where A is the total weight of drug in the tablets, r_0 is the initial radius of the tablet, D is the drug diffusion coefficient in the dissolution medium, ε and τ are the porosity and turtuosity of the matrix, respectively, and C_s is the solubility of the drug in the dissolution medium.

The values of the three shape factors were reported for spherical, cylindrical and biconvex tablets, and it was noted that for the spherical and cylindrical tablets the values of the three shape factors are constant and could be obtained from the initial dimensions of the dry tablets prior to dissolution. On the other hand, there is time dependent variation in the values of the three shape factors for biconvex tablets.

Subsequent experimental results showed that actual experimental drug release rates varied clearly with varying tablet shapes between cylindrical and biconvex, with the lower release being for biconvex tablets. However, no significant differences were noted between tablets with different shapes with regards to the drug release constants obtained from fitting the data to the proposed equation (Cobby et al 1974a, 1974b).

The actual implementation of such equations for the investigation of the drug release process from matrix tablets, including hydrophilic ones, should always take into account the influence of other hydration-associated phenomenon on the overall drug release process; processes affecting the integrity of the system during its dissolution like crack formation due to the relaxation of stresses formed within the tablets during the manufacturing process could enhance the drug release rate and cause considerable deviations from the theoretical outcomes.

Karasulu et al (2000, 2002) studied the release of Theophylline from HPMC tablets of different geometric shapes namely triangular, cylindrical and half spherical tablets and they compared the rate of drug release from the various tablets using the Higuchi model. They reported that the highest drug release rate was observed with the triangular tablets followed by the cylindrical ones and then the half-spherical.

The effect of tablet surface area on drug release has also been examined, and results obtained with flat HPMC tablets of varying radius

and convex tablets demonstrated that drug release rate was directly proportional to tablet surface area, and it was concluded that maximum control of drug release could be obtained when tablets are nearest to the spherical shape (Ford et al 1987). Siepmann et al (2000) studied several variables associated with cylindrical matrix tablets in terms of their effect on the release of Propranolol HCl and Chlopheniramine HCl from such tablets, and they reported that both varying the half height and radius of the cylinder had an effect on drug release. However, increasing the radius of the cylinder had a much more pronounced effect on the release of the drugs than increasing the half height of the cylinder and this was explained by the variation in the surface area of the cylinder and more precisely the surface area to volume ratio, which was more affected by changes in the radius than the half height of the cylinder.

In an extension of the previously mentioned work of Siepmann et al. Reynolds et al (2002) examined the effect of surface area to volume ratio on the release of three model soluble drugs from HPMC tablets made of different shapes, namely oval, round concave flat-faced bevelled edge, and flat faced round tablets, and they reported that surface area to volume ratio was more significant in controlling and predicting the release of the drugs from various tablets, they found that drug release from tablets with similar surface area to volume ratio was similar whether in tablets made of the same shape or among tablets of different shapes, whereas, tablets having similar surface areas but different surface area to volume ratios exhibited different drug release rates. Recently, similar

results were reported by Parojcic et al (2004) for tablets made with Carbopol; they found that tablet diameter is the major shape variable affecting drug release from the tablets, but for tablets manufactured with different heights or of different shapes, the relative surface area, which is the same as the previously mentioned surface area to volume ratio, could be more helpful in terms of comparison.

Other trends in increasing the area available for hydration have also been addressed for various tablet shapes. Ertan et al (1997) studied the effect of varying the surface area on the release of drug from a cylindrical implant. They adopted techniques such as coating and introduction of varying number of holes into the structure of the tablet, they reported that increasing the surface area available for hydration led to an increase in drug release. Similar results were observed by Cheng et al (1999) using donut-shaped HPMC tablets with varying number of holes.

1.1.6. Methods used in the evaluation of hydrophilic matrix dosage forms:

Due to the importance of the changes taking place within hydrophilic matrix dosage forms that are responsible for sustaining drug release, in vitro techniques have been developed to evaluate such dosage forms. Such techniques have focused primarily on studying the nature of structural changes and correlate them either qualitatively and quantitatively with the process of drug release.

Several techniques have been used to monitor the in vitro behaviour of hydrophilic matrix dosage forms, ranging from simple visual and imaging techniques to more sophisticated ones utilising modern microscopic, and non invasive methods. The following are some of the major techniques successfully employed in the investigation of hydrophilic matrix systems.

1.1.6.1. Macroscopic swelling studies:

Monitoring the extent of dimensional changes occurring within hydrophilic matrix systems is a major method utilised in the evaluation of, and comparison between various formulations and dosage forms. This is particularly important as such changes are usually highly correlated with the hydration patterns associated with hydrophilic matrix systems.

Simple methods in which visual monitoring of the expansion of the hydrophilic matrix dosage form takes place have been reported by several authors. The simplest of such methods depend on monitoring the expansion behaviour of matrix tablets upon placement in a hydration medium (Sujja-Areevath et al 1998, Talukdar et al 1995 , Parakh et al 2003).

For monitoring the swelling in the axial dimension, Panomusk et al (1995) developed a method in which a hydrophilic matrix tablet is placed in a test tube containing the hydration medium in a way that allows a single face of the tablet to be hydrated and hence swell. The increase in tablet height is

measured directly. One drawback of such method is the limited hydration and hindered swelling of the tablet. Talukdar et al (1995) used a dial indicator to measure the axial swelling of a tablet. However, they report that the weight of the indicator may impede the axial expansion of the tablet.

The use of photographic methods has also been reported for monitoring the swelling of hydrophilic matrix dosage forms. In their study, Sujja-Areevath et al (1998) used simple photography to monitor the axial swelling of matrix tablets.

Using photography to investigate the internal changes within a hydrating tablet in addition to the overall swelling is also possible. In a series of studies, Colombo et al developed a method in which a hydrophilic matrix tablet is placed between two plexiglass slides, thus allowing only radial water ingress and swelling to take place when introduced into a dissolution medium. This method enabled them to evaluate radial swelling, and also the movement of the various fronts within the hydrating tablet. To obtain clearer results, they incorporated a coloured drug into the matrix tablet which allowed better identification of the various regions inside the hydrating tablet (Colombo et al 1995, 1996, 1999).

Image capture and analysis systems have also been used successfully in monitoring the swelling of hydrophilic matrix dosage forms. Moussa et al used a method in which matrix tablets were placed in the hydrating

solution at a constant temperature, and at various time intervals a tablet was transferred to an image analysis apparatus in which the radial swelling is recorded directly and the axial after cutting the tablet into half. By using a source of light placed underneath the tablet, they were able to monitor the water concentration gradient across the tablet depending on the difference in the intensity of light transmitted through the various regions of the tablet (Moussa et al 1996, 1998). A similar method was used by Maggi et al to study the swelling of tablets made with different Polyethylene Oxides. They used a photographic camera with a microscope to take images of hydrating tablets after cutting, and the images where analysed with an image analysis software to measure the dimensions of the tablet and the gel layer (Maggi et al 2002). One major drawback of such techniques is the lack of live in situ measurements; the removal of the tablet from the hydration medium could alter the structure of the outer tablet surface. This problem was overcome in the method developed by Gao and Meury (1996) in which they used an image capture and analysis system to obtain live in situ images of hydrating tablets placed within a stirred medium. Samples from the medium were also withdrawn to study the release of drug from the tablet at various time intervals. However, it may be difficult to compare the results of such a method with of the studies due to the temperature at which the tablets were hydrated which is 22º Celsius.

Other techniques focused on live monitoring of the swelling of hydrophilic matrix tablets in situ. Quintanar-Guerrero et al (1999) developed a system

in which the tablet was placed in a stirred hydrating medium kept at 37º Celsius through a peristaltic pump. They monitored the swelling of the tablet by placing the hydration vessel on top of a projector and projecting the image of the swelling of the tablet on a wall, they also used still photography to obtain images of the swelling tablet.

Studying the dimensional changes occurring within a hydrating matrix dosage form enabled researchers to compare between various formulations through monitoring. Other methods described in the literature investigated matrix swelling in terms of weight changes occurring within the hydrating dosage form (Parakh et al 2003, Desai and Kumar 2004).

However, emphasis should be made that the process of weight change is not caused by water uptake only. It is a net process arising from several contributing factors, mainly water ingress into the dosage form, and a number of counteracting processes, namely the erosion of the polymer, and the release of the drug and other formulation ingredients. Thus consideration should be given to both the wet weight of the tablet and its weight after drying.

Recently, Baloglu et al (2004) investigated a new method for monitoring the swelling of hydrophilic matrix bioadhesive tablets using a technique based on spectrocolorimetry. Their method is based on the gradual change in the colour of hydrophilic matrix tablets during the hydration

process. One limitation of such technique might lie in the different properties of various formulations in terms of the extent and nature of colour change. This may limit the applicability of such system in the comparison between different formulations.

1.1.6.2. Microscopic studies:

Several microscopic techniques have been adapted and used to investigate the behaviour of hydrophilic matrix dosage forms. Such techniques enabled more insight into the behaviour of such dosage forms, through enabling the visualisation, and monitoring of structural changes, and movements taking place within the dosage form. This had particular advantage for investigating the hydrated gel layer.

Simple light microscopy was used to compare the thickness of the gel layer formed on the radial faces of hydrating slabs formulated with different polymers. Such method had the advantage of avoiding the swelling restrictions applied by the previously mentioned plexiglass method. However, the gel layer formed on the axial face of the slabs had to be removed to obtain a clear picture using the microscope. Such manipulation may give rise to significant alterations in the actual structure of the gel layer (Zuleger et al 2002).

Scanning electron microscopy (SEM) has been employed successfully in the study of hydrophilic matrix dosage forms. In their investigation of the

deferring behaviour of sodium alginate matrices when placed in simulated gastric fluid or simulated intestinal fluid, Hodsdon et al (1995) used cryogenic scanning electron microscopy. The results obtained with this technique revealed a difference in the nature of the gel layer formed by such matrices in the different media; it was tough and porous in simulated gastric fluid and highly hydrated and continuous in simulated intestinal fluid. Moreover, the difference in the hydration pattern across the gel layer formed within simulated intestinal fluid was also observed; cryogenic scanning electron microscopy showed that it was extensive at the outer surface of the gel layer, whereas it was less extensive and less regular in the inner region of the gel layer.

The source of gas bubbles, usually associated with the hydrated gel layer formed within hydrophilic matrix dosage forms, was investigated in Xanthan Gum and HPMC matrices using optical microscopy and cryogenic SEM which revealed their accumulation in the region near the interface between the core of the matrix and the rest of the gel layer (Melia et al 1993).

Scanning electron microscopy was also used to study the interactions between the different ingredients of the hydrophilic matrix system. Katzhendler et al (1998, 2000) used Scanning electron microscopy to investigate the different release patterns of the drug Carmazipine from hydrophilic matrix systems formulated using HPMC or egg albumin. They revealed that the polymeric carriers had different effects on the crystalline

properties of the drug within the hydrated gel layer of the tablet which led to different behaviour of the two matrix systems.

Another technique that has been adapted to study hydrophilic matrix dosage forms in confocal laser scanning microscopy (CLSM). This technique presents several advantages over normal microscopic technique including the ability to visualise internal structural properties and changes within a system without the need to physically cutting it, and without interference from out of focus light which produces clearer images (White et al 2005). In the area of hydrophilic matrix dosage forms, several studies report the use of this microscopic technique. Alder et al (1999) tried to quantify the dimensional expansion of hydrophilic matrix tablets formulated with Xanthan Gum and HPMC by using CLSM. Cutts et al evaluated the diffusion of a fluorescent compound in a hydrating hydrophilic matrix through monitoring the rate and shape of recovery of a bleached florescent spot (Cutts et al 1996). The ingress of fluorescently labelled water into hydrophilic matrix tablets was also investigated using CLSM (Bajwa et al 2006).

However, some limitations are encountered when using technique, namely the usual low penetration power of the used laser beam which could hinder its use in the investigation of whole tablet structures. Moreover, the possible interaction of the ionic fluorescent materials used in this technique with formulation ingredients within the matrix system may give rise to artefacts and unexpected behaviours.

1.1.6.3. Magnetic resonance studies:

Nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) are non-invasive techniques that have been used by several groups in an attempt to study various aspects of the behaviour of hydrophilic matrix systems.

Rajabi-Siahboomi et al (1994) used NMR-imaging to probe the swelling of different varieties of HPMC, and this technique enabled them to monitor the expansion of both the forming gel layer and the core of the tablet, They reported that in terms of gel layer formation, the effect observed was the same in both the axial and radial directions. However, expansion of the tablet core was only observed in the axial direction. Moreover, they observed that the hydration of the edges of the tablets was more pronounced leading to the formation of a concaved gel layer. Similar results regarding the faster hydration of tablet edges were also reported by Botwell et al (1994).

Fyfe et al (1997) compared the swelling of two matrix tablets with different thickness using NMR imaging and they found that the swelling behaviour was similar for both tablets during the initial hydration, but when the thinner tablet became fully hydrated it underwent faster swelling.

Kojima et al (2002) used MRI to compare water mobility in matrices prepared using different ethyl cellulose derivatives, and they report that in all matrices the mobility of water is dependent upon the location within the

matrix system; on the outer surface water mobility was similar to that of free water whereas near the core of the tablet was highly restricted. MRI images also allowed the monitoring of dimensional changes within the hydrating tablets. When comparing the growth of the gel layer they found that it was different between the various cellulose ethers used with Hydroxypropyl Cellulose having the thickest gel layer. The reported observation of a water mobility gradient across the gel layer agrees with earlier results obtained by Rajabi-Siahboomi et al (1996) with HPMC matrices.

1.1.6.4. Dissolution and erosion studies:

In vitro dissolution studies form a major part in the evaluation of hydrophilic matrix dosage forms. Analysing the process of drug release from such dosage forms usually comprises the main aspect of comparison between various systems.

Several dissolution techniques have been used in the evaluation of drug release from hydrophilic matrix dosage forms, each with its advantages and disadvantage. The USP paddle method is one of the predominant methods used, with various rotation speeds. This method could provide the advantage of unhindered swelling especially for larger dosage forms. However, its use with certain dosage forms is considered problematic by some studies, especially with sticking and floating dosage forms. This is due to the limited surface area, within the dosage form, that is available

for contact with the hydrating medium, and hence for drug release (Melia 1991).

The USP basket method has also been used in the evaluation of hydrophilic matrix dosage forms. However one main disadvantage of this method could arise when using larger dosage forms, and is due to the hindered swelling of the systems because of the limited size of the basket (Melia 1991).

Monitoring the release of hydrophilic polymer from the dosage form through erosion studies is also of importance, especially with systems in which the erosion process is enhanced, or could contribute significantly in the process of drug release. Several studies have reported the use of erosion studies where the hydrophilic matrix dosage form is withdrawn from the dissolution medium at consecutive time intervals and the weight difference calculated after drying the dosage form is used in the evaluation of the erosion process (Sujja-Areevath et al 1998, Munday and Cox 2000).

It becomes evident that each of the previously mentioned techniques presented certain advantages, and enabled the investigation of particular processes occurring within hydrophilic matrix system. Hence, the use of a combination rather than single methods would provide a clearer picture about the in-vitro behaviour of hydrophilic matrix systems, including tablets.

1.1.6.5. Methods used in the evaluation of the dissolution patterns from hydrophilic matrix dosage forms:

Initial work by Higuchi (1963) intended to describe the release of drugs from planar matrix systems, and he produced a model (Equation 1.3.) describing drug release from a planar system formed of a homogeneous matrix, assuming perfect sink conditions apply throughout the release process.

$$Q = (\underline{D}(2\underline{A}-C_s)C_s t)^{1/2} \qquad \textbf{Equation 1.3.}$$

where Q is the amount of drug released at time t per unit area of the planar matrix system, $\underline{A}$ is the initial amount of drug in the system, C_s is the solubility of the drug in the penetrating medium and $\underline{D}$ is the diffusivity or diffusion constant of the drug in the matrix (polymer).

A modified version of the previous equation is used to express drug release from granular matrices in order to accommodate for the difference in the effective diffusional path (Equation 1.4.):

$$Q = (\underline{D}\varepsilon/\tau\ (2\underline{A} - \varepsilon C_s)\ C_s t)^{1/2} \qquad \textbf{Equation 1.4.}$$

where τ is the tortuosity factor of the system, and ε is the porosity of the system (Higuchi 1963).

From the previous two equations it is clear that modifying the release of a drug from a matrix system can be achieved through modifying several factors; the initial concentration of drug within matrix, the polymer forming the matrix system, the porosity and tortuosity of the matrix system and the solubility of the drug.

A simple version of the Higuchi model (Equation 1.5.) is used by most studies:

$$Q = k\, t^{1/2} \qquad \textbf{Equation 1.5.}$$

where K is the dissolution rate constant of the drug.

Korsmeyer et al (1983) introduced an exponential equation (Equation 1.6.) describing the release of a solute from controlled release devices.

$$M_t/M_\infty = kt^n \qquad \textbf{Equation 1.6.}$$

where M_t is the amount of drug released at time t, M_∞ expresses the total amount of drug present in the device, k is a constant related to the properties of the system and the drug, and n is the “diffusional exponent” (Korsmeyer et al 1983).

Peppas et al applied the previous equation to study the first 60% of drug release from various devices, and they reported that the value of n could

vary with the geometry of the controlled release device; for pure diffusional release (Fickian Diffusion) the value of n is 0.5, 0.45 and 0.43 for thin films, cylinders and spheres respectively. When other mechanisms such as polymer relaxation are involved in the process of drug release (anomalous or non-Fickian drug transport) the value of n is increased until it reaches a value where drug transport is said to be of case II transport in which the major mechanism governing the transport process is polymer relaxation, and they reported different ranges for the value of n for different controlled devices shapes. (Peppas 1985, Ritger and Peppas 1987a, 1987b).

In further development of their equation, and depending on the results they obtained which show that the value of n for case II drug release is about twice the value for pure Fickian diffusion, Peppas and Sahlin (1989) introduced a modified version of their previous formula with separate terms expressing the contribution of Fickian and relaxation processes (Equation 1.7.).

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m}$$ **Equation 1.7.**

The first term of the equation expresses the contribution of the Fickian diffusion process, whereas the second expresses the contribution of the relaxation process in drug transport. k1 and k2 are constants related to the diffusion and relaxation processes respectively, and m is the Fickian diffusion exponent for a controlled release device of any shape. From this

equation the relative contribution of both mechanisms on the process of drug transport can be calculated according to the following equation (Equation 1.8.):

$$R/F = (k_2/k_1) \times t^m \qquad \textbf{Equation 1.8.}$$

where R and F are the percentage contributions of Relaxation and Fickian processes respectively (Peppas and Sahlin 1989).

One major limitation associated with all of the previously mentioned model-dependent approaches, lies in the fact that they are mainly deducted from a limited portion of the drug release profile. Moreover, such models usually overlook the initial phase of drug release, the so called “burst effect” which could lead with some formulations to the release of a considerable amount of drug from the dosage form.

Other published work has focused on studying the potential for model dependent approaches in the investigation of the hydration and erosion aspects of hydrophilic matrix systems. Tahara et al (1995) proposed two equations for the infiltration of the hydration medium into HPMC tablets, and the erosion of the matrix from such tablets. According to their results the ingress of the hydration medium into HPMC tablets could be described in terms of the square root law proposed by Higuchi according to equation 1.9.

$Q_w = k_1 t^{1/2}$ **Equation 1.9.**

where Q_w is the percentage of the hydration medium in the matrix, k_1 is a rate constant describing the infiltration of the hydration medium into the interspace of the tablet.

On the other hand, the process of matrix erosion was described in terms of a qube root equation (Equation 1.10.).

$$\left(\frac{W_d}{W_i}\right)^{1/3} = 1 - k_2 t$$ **Equation 1.10.**

where W_i is the initial dry weight of the tablet, W_d is the dry weight of the tablet after immersion for a specified time in the hydration medium, and k_2 is a rate constant describing the erosion of the tablet.

Siepmann and Peppas (2001) discussed the overall process of drug release from HPMC systems including polymer erosion from such systems. They stated that above a critical water concentration resulting from the ingress of the hydration medium into the system, polymer chains located at the surface of the system start to disentangle and diffuse into the surrounding hydration medium. Thus the process of erosion could be expressed in terms of polymer diffusion according to equation 1.11.

$M_{pt} = M_{p0} - k_{diss} A_t t$ **Equation 1.11.**

where M_{pt} and M_{p0} are the weights of the dry matrix at time t and 0, respectively. k_{diss} is a rate constant describing the loss velocity of the polymer from the system, normalised to the surface area of the system at the specified time point which is A_t.

One possible source for considerable deviations from such an equation is embedded in the formulation of hydrophilic matrix systems, which usually contain a number of materials in addition to the matrix forming polymer. The presence of such materials in the hydrated matrix, especially the ones with low solubility in the hydration medium, may affect the integrity of the overall hydrated matrix and enhance the erosion process even before the polymer chains reach their disentanglement concentration.

1.2. Influence of tablet face curvature on the properties of pharmaceutical tablets:

Tablets continue to constitute a major part of available pharmaceutical dosage forms as they present several advantages over other pharmaceutical dosage forms, mainly the ease of their production which is accompanied by the ability to control the stability, amount, and properties of the active ingredients incorporated in them. Moreover, tablets could be produced using a variety of techniques, and they offer an easy and safe manner for drug delivery (Alderborn 2002). Tablets are available in a variety of shapes for multiple reasons associated with manufacturing, identification and ease of use. The majority of available

tablets are round or capsule shaped with varying degree of face curvature.

The introduction of a certain degree of face curvature to pharmaceutical tablets could have a profound influence on the physical properties of the tablets. Several workers in literature have focused on investigating the impact of tablet face curvature on the various physical and structural properties associated with the tablets (Eiliazadeh et al 2003, Sinka et al 2004, Sugimori et al 1989, Pitt et al 1988, 1989).

Variations in the face curvature of pharmaceutical tablets lead to significant variations in the density distribution within the tablet. Various methods have been employed in the investigation of this phenomenon. Eiliazadeh et al (2003) investigated radial and axial powder movements within the powder column during powder compaction, and the resulting density distribution in flat and convex tablets formulated with microcrystalline cellulose, by introducing a coloured layer into the structure of the tablets and using image analysis to investigate the density distribution. They noted that the density distribution was not homogenous in both flat and convex tablets, with higher density regions occurring within tablet parts in contact with the die wall due to friction forces. They also noted that density variation increased with the increase in compaction pressure. Moreover, they showed that the density distribution was different between flat and convex tablets, as the effect of die wall friction was more noticeable in convex tablets. This lead to higher

degrees of stress relaxation in convex tablets, leading to lamination which originated within the weaker sections located in the centre of the convex tablets. Similar findings in terms of density variation within flat and convex tablets had also been noted using a technique based on gamma radiation attenuation which was influenced by the density variation within the tablet (Charlton and Newton 1985).

Sinka et al (2004) used X-ray Microtomography to get a profile of density distribution within capsule shaped tablets of varying cup geometry. They found that considerable variations in density distribution were present within the same tablet, and between tablets with different cup geometry. However, they also stated that density distribution investigations should not be used as a generalised rule due to the multiple factors, associated with material properties, tablet properties, and the actual compaction process, which could influence the compaction patterns within the different tablets. Recently Djemai and Sinka (2006) reported similar findings with regards to density variations within and between tablets using NMR imaging of round and capsule shaped microcrystalline cellulose tablets.

The direct compression process of tablets with different degrees of face curvature, and the influence of die wall pressure on tablet properties were also investigated. Sugimori et al (1989) monitored the die wall pressure resulting during the compression of both flat and convex tablets and they reported higher residual wall pressure towards the end of tablet

decompression, in the case of convex tablets. Moreover, this phenomenon was noted in certain tablets which where characterised by having a smaller height. The higher values of residual wall pressure were also associated with the occurrence of capping within the tablets which resulted ultimately in a drop in the value of residual wall pressure in the case of convex tablets as compared to flat ones.

Another important aspect which has been investigated, and shown to be influenced by the change in tablet face curvature, is tablet tensile strength. The change in tablet face curvature was reported to cause significant variations in the tensile strength of round tablets (Pitt et al 1988, Pitt et al 1989, Newton et al 2000a). Such variations could be attributed to variations in powder movement within tablets with different face curvature during compression, and thus to the previously mentioned variation in the density distribution within the tablets and its potential to influence the formation and propagation of cracks within the tablet structure. Similar results were also reported with elongated tablets, in which variations in the height of tablet face curvature led to clear variations in the tensile strength of the tablets (Newton et al 2000b).

The influence of tablet face curvature on other physical properties associated with pharmaceutical tablets has also been studied. Chowhan et al (1992) studied the influence of tablet face curvature on the friability of round tablets. They suggested that the influence of tablet face curvature on tablet friability is characterised by the presence of a “critical

level" for tablet face curvature, above which tablet friability was noticeably reduced. However, no differences were noted between tablets with lower degrees of face curvature.

1.3. Aims and objectives:

A limited amount of literature is available about the influence of tablet face curvature on the properties of matrix tablets, more specifically, hydrophilic matrix tablets. Recently Pajander et al (2006) investigated the hydration patterns of cylindrical and convex tablets using the hydrophobic starch acetate as a matrix former. They noted different hydration patterns associated with cylindrical and convex tablets. They also studied the process of crack formation within the tablets and correlated this with the dissolution properties of these tablets. With respect to hydrophilic matrix tablets, Djemai et al (2005) studied the occurrence of cracks in round HPMC convex tablets with two degrees of face curvature, manufactured using both a single punch press and a rotary tablet press. In addition to investigating the use of NMR imaging as a tool to detect internal structural defects in convex tablets, they correlated the presence of such defects with the bursting of some convex tablets during tablet hydration.

The previous studies investigated certain phenomena occurring within round convex tablets with particular degrees of face curvature, and formulated using a single formulation. However, tablets, including hydrophilic matrix based ones, could be made from multiple formulations

using different ingredients. Moreover, tablets could be made with different shapes and different degrees of face curvature. These variables could affect the behaviour of the tablets, whether in their dry state, or upon hydration. Moreover, the hydration of hydrophilic matrix tablets encompasses multiple features, especially tablet structural expansion and the formation of the gel layer on the tablet surface. Thus, investigating the impact of changing tablet shape and structural properties and the properties of the formulation used in tablet production need to be done concurrently, as their influences on tablet integrity, hydration and dissolution characteristics could be highly correlated.

The overall aim of this work was to study the influence of dosage form variables, in terms of tablet face curvature and tablet overall porosity, and the type of formulation used on the overall in-vitro behaviour of both round and elongated hydrophilic matrix tablets. Multiple degrees of tablet face curvature and tablet overall porosity, and different formulations were used with both tablet shapes to be able to describe the influence of these variables comprehensively.

The objectives of the work were the investigation of the influence of the studied factors on the physical properties of the tablets in their dry state, monitoring the structural changes occurring within the tablets upon hydration, and the differences in such changes between the different tablets studied. A further objective was to correlate the nature of the structural changes occurring within the hydrating tablets with the nature

and properties of the gel layer formed within the various tablets. Another objective of the study was to investigate the influence of the studied variables and the resulting structural variations within the tablets, in their dry and hydrated states, on the dissolution characteristics of the two drugs from the various tablets.

Finally, one objective of the study was to explore the potential use of statistical analysis techniques in the investigation, comparison, and presentation of the in-vitro behavioural patterns associated with hydrophilic matrix tablets with different structural and formulation properties.

CHAPTER TWO

2. Materials and Methods:

2.1. Materials:

2.1.1. Xanthan Gum:

Xanthan Gum is an anionic polysaccharide produced by the gram positive bacteria *Xanthomonas campestris*. It has a high molecular weight of about 2 x 10^6. The chemical structure of Xanthan Gum consists of repeating pentasaccharide units each containing two glucose residues, two mannose residues and one glucoronic acid residue. The backbone of the polysaccharide is virtually identical to that of cellulose; formed of β-D-glucose units linked together at the 1 and 4 positions. However, the Xanthan Gum structure differs from that of cellulose by the presence of a trisaccharide side chain, formed of two mannose residues and one glucoronic acid residue, and attached to each alternate glucose residues at the 3rd position. Most of the mannose residues at the terminal position of the side chain have a pyruvate moiety and the mannose residues closest to the backbone could be acetylated at the 6 position (Lachke 2004, Singh 2006)

The usual chain structure of Xanthan Gum could exist as a single, double or triple helix. The helical structures of adjacent Xanthan Gum molecules can interact, giving rise to a weakly bound network (Singh 2006).

As a powder Xanthan Gum occurs as a cream or white coloured free flowing powder which is mainly fine in size. It is soluble in cold and warm water but practically insoluble in ethanol and ether (Singh, 2006).

The intrinsic ability of Xanthan Gum to form weak gel structures gives rise to its wide applications. It is used as a thickening agent and emulsifier in the food and confectionary industry due to its lack of toxicity. It has also applications as a stabilizer, emulsifier and suspending agent in many industries, including cosmetics, agriculture, paint production, ceramics and textile (Lachke 2004).

In terms of its pharmaceutical applications, Xanthan Gum is used in the production of hydrophilic matrix systems, mainly tablets. It has been reported that Xanthan Gum gives rise to stable gel structures that give almost zero order drug release (Dhopeshwarkar and Zats, 1993). Xanthan Gum is also used in the production of topical formulations due to its shear thinning behaviour. It also has applications in the production of ophthalmic and vaginal dosage forms.

Xanthan Gum used in this study was a kind gift from A and E Connock perfumery and confectionary Ltd. (Fordingbridge, England). The batch number is 165558.

2.1.2. Spray dried lactose:

Spray dried lactose is a white or off-white powder, which is mainly odourless, and has a high aqueous solubility of 1 part in 4.63 parts of water (Kibbe 2000). It consists of spherical particles that contain a mixture of crystalline and amorphous lactose entities, containing α-lactose and β-lactose moieties. It is usually produced by a process of spray drying in which a suspension of α-lactose monohydrate crystals, containing approximately 10-20% of dissolved lactose and 80-90% of suspended particles in the crystalline form is used.

Spray dried lactose is used mainly as a diluent in the production of pharmaceutical tablets by direct compression, due to its good compaction properties. It had been reported that the compaction and flow properties of this type of lactose are highly affected by its particle size and the proportion of amorphous content in the particles (Vormans et al 1987). The spray dried lactose used in this study is Zeparox® which was supplied by Borculo Whey Products (Needsweg, Holland). The batch number is 642708.

2.1.3. Dibasic Calcium Phosphate Dihydrate (Emcompress®):

Dibasic calcium phosphate dihydrate is a white odourless and tasteless powder or crystalline solid that is practically insoluble in ethanol, ether and water, but soluble in dilute acids. It is available in two particle size ranges, the finer of which (milled) is used mainly in wet granulation. The coarse grade is used in the direct compression of tablets due to its good flow behaviour and its desirable compaction properties; it deforms mainly by brittle fracture (De Boer et al 1978, Moreton 2006). The dibsaic calcium phosphate dihydrate used in this study is Emcompress®. It was supplied by JRS Pharma Ltd. (Surrey, UK). The batch number is 515H.

2.1.4. Magnesium Stearate:

Magnesium stearate is a very fine white cohesive powder with poor flowability (Allen and Luner, 2006). It consists of a mixture of magnesium salts of various fatty acids, predominantly stearic acid and palmitic acid, with minor proportions of other fatty acids. The powder is present in three degrees of hydration; trihydrate, dihydrate and anhydrate. It is practically insoluble in ethanol, ether and water (Allen and Luner, 2006). In the pharmaceutical industry magnesium stearate is mainly used as a lubricating agent in the formulation and production of tablets and capsules at concentrations between 0.25 and 5.00 % w/w (Allen and Luner 2006). The magnesium stearate used in this study was supplied by BDH chemical Ltd. (Pool, England). The batch number is 555174.

2.1.5. Orphenadrine Citrate:

Orphenadrine Citrate is a cationic drug. It exists in the form of a white or almost white crystalline powder. It is sparingly soluble in water, with an aqueous solubility of 1 part in 70 parts of water. It has a molecular weight of 461.5 g/mol, and a melting point of 134°C to 138°C (Moffat et al 2004). Orphenadrine Citrate salt used in this study was supplied by Sigma-Aldrich Company Ltd. (Chillingham, UK). The batch number is 048f0510.

2.1.6. Orphenadrine Hydrochloride:

Orphenadrine Hydrochloride is a cationic drug. It exists in the form of a white or almost white crystalline powder (BP 2007). It is freely soluble in water, with an aqueous solubility of 1 part in 1 part of water. It has a molecular weigth of 305.9 g/mol, and a melting point of about 156°C to 157°C (Moffat et al 2004). Orphenadrine Hydrochloride used in this study has a purity ≥ 98%. It was supplied by Fluka Chemie GmbH, (Italy). The lot number is 1093843.

The drug Orphenadrine has a pK_a of 8.4, thus it is expected to have a higher solubility at lower pH values due to the ionisation of the drug.

2.1.7. Distilled de-aerated water:

The water used in this study, was distilled water, de-aerated using a bench dissolution media preparation unit (Copley Degasser, Copley

Scientific Ltd., Nottingham, UK). Media de-aeration was done at 37°C by subjecting the required volumes of distilled water to a constant vacuum with constant stirring.

2.2. Methods:

2.2.1. Particle size analysis:

Particle size analysis for the powders used in the study was done using light microscopy. A small sample of each powder was placed on a glass slide, and dispersed in 2-3 drops of dispersion liquid. A set of dispersion liquids with refractive indices ranging from 1.40 to 1.70 were tested (Certified refractive index liquids, Calligen, USA), in order to acquire suitable contrast between the particles of each powder and the background. For spray dried lactose, Emcompress®, and Orphenadrine HCl, a dispersion liquid with a refractive index of 1.40 was used and for Xanthan Gum and Orphenadrine Citrate, a dispersion liquid with a refractive index of 1.70 was used. The powder sample was mixed thoroughly with the dispersion liquid to achieve maximum particle dispersion and minimize the presence of any powder agglomerates. A slide cover was introduced slowly on top of the dispersed powder to minimize the formation of any air bubbles.

The particle size analysis was carried out using light microscopy (Olympus BH-2, Olympus Optical Co., Japan). An objective lens with a magnification power of 4X was used for the investigation of Xanthan

Gum, spray dried lactose, Emcompress® and Orphenadrine Citrate samples resulting in a total resolution of the combined microscope and image analysis system of 50X. For the investigation of Orphenadrine HCl an objective lens with a magnification power of 10X was used, resulting in a total resolution of 125X. Multiple pictures of the microscope field were acquired using a digital camera connected to the microscope (Axiocam MRC, Carl Zeiss GmbH, Göttingen, Germany). The pictures were then automatically analysed using image analysis software (KS 400, Carl Zeiss GmbH, Göttingen, Germany). The software was initially calibrated using a graduated slide (S16 Stage Mic. 1mm/0.01 Div., Graticules Pyser-SGI Ltd, Kent, UK). Images of the powder systems were processed automatically. Initially a threshold was set to allow the clear visualisation of particle boundaries and to minimize the influence of background noise. A black and white image was produced and individual particles were then analysed for a set of three size parameters; particle projected area, particle minimum Feret diameter and particle maximum Feret diameter. A minimum of one thousand particles were analysed for each powder system.

Prior to the final measurement process, each black and white image was subjected to manual processing to minimise the influence of artefacts; particles on the borders of the image, air bubbles, and regions in which agglomeration was apparent were marked and rejected from the analysis process.

2.2.2 Determination of the moisture content of the powders:

The determination of powder moisture content was carried out using halogen moisture analysis which provided a rather fast and reliable procedure for moisture content determination. A powder sample of 4-5 g in weight was dispersed evenly on a flat aluminium tray. The tray was introduced into the heating chamber of a halogen moisture analyser (HG 53 Halogen Moisture Analyser, Mettler Toledo GmbH, Switzerland). Sample heating was carried out at a temperature of 90°C for all powders apart from magnesium stearate which has a reported melting point of about 60°C, hence a heating temperature of 50°C was used for this powder. The moisture analyser had a built-in scale and the reduction in sample weight to 0.001 g was monitored at 30 seconds intervals. The analyser was programmed to switch off automatically when the reduction in sample weight was less than 1 mg every 140 seconds, which was considered as stable dry weight.

2.2.3. Determination of the apparent density of the powders:

Helium pycnomtery was used to determine the apparent powder density for each of the powders used in this study. A single chamber helium pycnometer was used (Multipycnometer, Quantachrome Corp., NY, USA). The pycnometer was initially switched on and allowed to warm up for thirty minutes. Helium was then introduced into the measurement chamber and allowed to purge for ten minutes. Calibration of the pycnometer was carried out using two small calibration spheres with a

volume of 1.078 cm^3 each. Powder samples were accurately weighed and introduced in the pycnometer chamber for analysis. Five different powder samples were analysed for each material used, and each sample was further analysed five times, the mean value of which was used in the calculation process.

2.2.4. Calculation of tablet volumes:

2.2.4.1. Round tablets:

The volume of flat round tablets used in the study was calculated using Equation 2.1.

$$V_t = \pi r^2 t \qquad \textbf{Equation 2.1.}$$

where (V_t) is the volume of the tablet, (r) is the radius of the tablet and (t) is the height of the tablet.

The volume of convex round tablets includes the volume of the cylindrical portion of the tablet which was calculated using Equation 2.1., and the volumes of the two convex caps of the tablet (see figure 2.1.), each of which was calculated using Equation 2.2.

$$V_c = \frac{1}{3}\pi h^2 \left(3R - h\right) \qquad \textbf{Equation 2.2.}$$

where (V_c) is the volume of the cap, (h) is the height of the cap and (R) is the radius of tablet curvature.

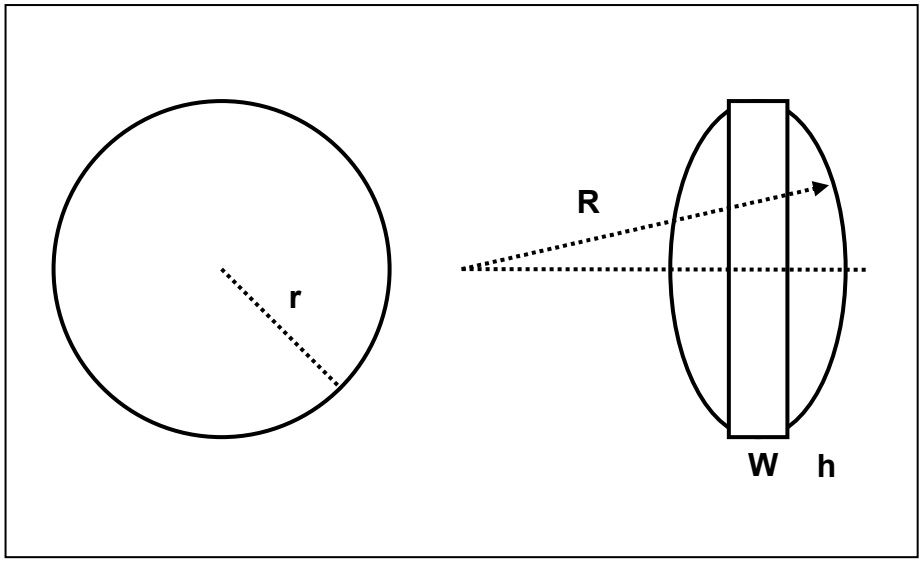

Figure 2.1. Schematic representation of the dimensional parameters of round tablets, R: radius of curvature, W: height of cylindrical part of the tablet, h: height of tablet cap, r: tablet radius.

2.2.4.2. Elongated tablets:

The volume of flat elongated tablets was calculated using equation 2.3.. The volume of convex elongated tablets includes the volume of the flat box and the volumes of two curved segments (see Figure 2.2.) which in turn was calculated according to equation 2.4..

$$V_t = b \times l_t \times d$$ **Equation 2.3.**

where (V_t) is the volume of the tablet, (b) is the tablet width, (l_t) is the tablet length and (d) is the height of the tablet.

$$V_{ce} \approx \left(\frac{2}{3} ba + \frac{a^3}{2b} \right) \times l_t$$ **Equation 2.4.**

where (V_{ce}) is the volume of the curved segment, (b) is the tablet width and (a) is the height of the curved segment

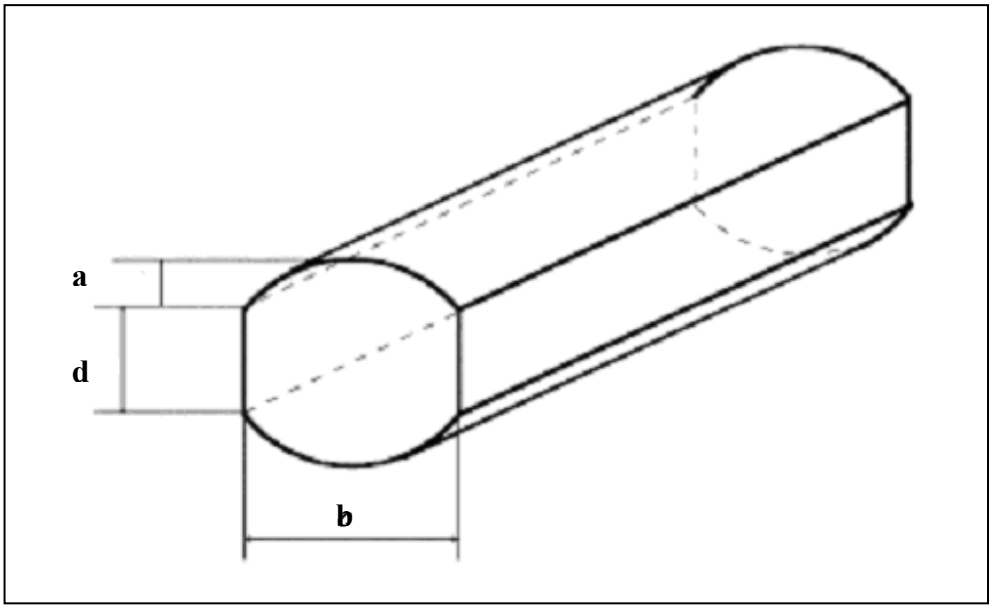

Figure 2.2. Schematic representation of the size parameters of elongated tablets, adapted from Newton et al (2000b), b: tablet width, d: height of rectangular tablet section, a: height of curved segment.

2.2.5. Calculation of tablet densities and weights:

Initially the densities of all tablets used in this study were calculated depending on the apparent densities of the powder mixtures used in tablet production, and the pre-determined porosities of the tablets (Equations 2.5. and 2.6.).

$$\rho_{mix} = \sum \rho_{powder} \times X_{powder}$$ **Equation 2.5.**

$$1 - \varepsilon = \frac{\rho_{tab}}{\rho_{mix}}$$ **Equation 2.6.**

where (ρ_{mix}) is the powder mixture density, (ρ_{powder}) is the density of the individual powders, (X_{powder}) is the percentage fraction of each powder in the powder mix, (ρ_{tab}) is the tablet density and (ε) is the tablet porosity.

The weights required for tablet productions were then calculated using the previously calculated values of tablet volume and tablet density (Equation 2.7.).

$$W_{tab} = V_{tab} \times \rho_{tab}$$ **Equation 2.7.**

where (W_{tab}) is the weight of the tablet, (V_{tab}) is the volume of the tablet and (ρ_{tab}) is the density of the tablet.

2.2.6. Production of tablets:

Initially, powder mixing was carried out in a step-wise process; all formulation ingredients apart from magnesium stearate were accurately weighed, and pre-mixed in a Turbula® mixer (Turbula, Basel, Switzerland) for six minutes. The powder mixture was then passed

through a 250μm mesh to break up any powder agglomerates. Any large un-agglomerated particles remaining on the mesh were then returned to the mixture. Afterwards, the powder mixture was further mixed in the Turbula mixer for another six minutes, before adding the required amount of magnesium stearate which was mixed with the rest of the powders for a further three minutes.

Tablet production was carried out using a process of direct compression. A single punch tablet press was used in the production of all tablets used in this study (F-press, Manesty Machines, Liverpool, England). For round tablets a die with an internal diameter of 12.5 mm was used. Four sets of punches with a progressively increasing face curvature ratio were used. All punches had a diameter of 12.5 mm. For elongated tablets, a die with a width of 10 mm and length of 25 mm was used. For the production of these tablets three sets of elongated punches were used with a width of 10 mm, length of 25 mm and a progressively increasing face curvature. All dies and punch sets were produced by the same manufacturer (I Holland Ltd., Nottingham, England).

Powder samples were accurately weighed depending on the calculated values of tablet weight. Each weighed sample was individually fed into the required die. The surface of the powder was then levelled using a small metal spatula, and the tablet was produced by manually operating the tablet press.

After ejection from the die, each tablet was accurately weighed to 0.0001 g, and the dimensions of the tablet were measured to 0.001 mm using a digital micrometer (Mitutoyo digital micrometer, Mitutoyo, Kawasaki, Japan). The height of the cylindrical part of round convex tablets, and the length and box height of elongated tablets were measured to 0.01mm using a digital calliper (UPM digital calliper, United Precision Machine Inc., Shenzhen, China). Weight and dimension limits were applied as a quality control procedure, in order to maintain a narrow margin of variation in tablet properties. Only tablets with weight variation within ± 0.01 g and dimensional variation within ± 0.01 mm from the theoretically calculated values were used in the study.

After production, each batch of tablets was stored in an amber glass air-tight container in a dark place at ambient conditions. Tablet storage was carried out for a minimum period of 14 days, to allow complete relaxation of tablets after the compaction process.

2.2.7. Determination of tablet tensile strength;

2.2.7.1. Round tablets:

Prior to use, the weights and dimensions of all tablets were determined to 0.0001 g and 0.001 mm respectively, and the height of the cylindrical part of convex tablets was measured to 0.01 mm. The breaking loads for round tablets were determined by subjecting the tablets to diametral loading between the two steel plates of a strength tester (CT 40,

Engineering Systems, Nottingham, UK). The load was applied at a rate of 1 mm/min, and the load at which tablet failure occurred was recorded. Tablets were inspected for their failure patterns after retrieval, and only tablets with a diametral failure pattern were used for evaluation.

The tensile strengths of flat round tablets were calculated using Equation 2.8. which was proposed by Fell and Newton (1968, 1970).

$$\sigma_t = \frac{2P}{\pi D t} \qquad \textbf{Equation 2.8.}$$

where (σ_t) is the diametral tensile strength of the tablet, (P) is the breaking load, (D) is the diameter of the tablet, (t) is the thickness of the tablet.

The tensile strengths of convex round tablets were calculated using Equation 2.9., developed by Pitt et al (1988).

$$\sigma_t = \frac{10P_s}{\pi D^2}\left(2.84\frac{t}{D} - 0.126\frac{t}{W} + 3.15\frac{W}{D} + 0.01\right)^{-1} \qquad \textbf{Equation 2.9.}$$

where (σ_t) is the diametral tensile strength of the tablet, (P_s) is the breaking load, (D) is the diameter of the tablet, (t) is the total height of the tablet and (W) is the height of the cylinder.

2.2.7.2. Elongated tablets:

In a similar manner to round tablets, the weights and dimensions of elongated tablets were determined to 0.0001 g and 0.001 mm, respectively, and the length and box height of curved elongated tablets were measured to 0.01 mm. The flexural breaking load of the tablets was measured using a physical testing instrument (CT 5, Engineering Systems, Nottingham, UK) fitted with a 3 point bending device (Figure 2.3.). The distance between the two lower rolls (a) was set at 16.5 mm, and the breaking load was applied at a rate of 1 mm/ min. The load at which tablet failure occurred was recorded using the peak hold facility of the strength tester. The failure patterns of the tablets were monitored after retrieval and only tablets in which the breaking was initiated at the centre of the lower surface were evaluated.

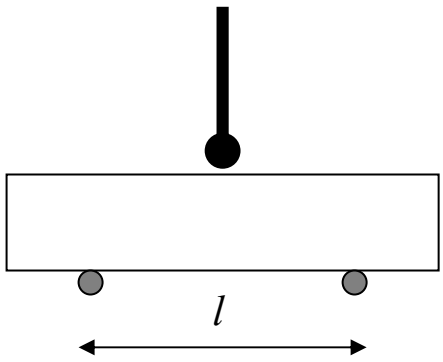

Figure 2.3. Schematic illustration of the bending test to determine the fracture load of elongated tablets.

The tensile strengths of flat faced elongated tablets were calculated using Equation 2.10. (Stanley and Newton, 1980).

$$\sigma_f = \frac{3Fl}{2bd^2}$$ **Equation 2.10.**

where (σ_f) is the flextural tensile strength of the tablet, (F) is the breaking load, (l) is the distance between the two lower rolls, (b) is the width of the tablet and (d) is the thickness of the tablet.

The tensile strengths of curved elongated tablets were approximated using Equation 2.11. (Stanley and Newton, 1980).

$$\sigma_f \cong \frac{3Fl}{2d^2}\left(\frac{d+2a}{6A+bd}\right)$$ **Equation 2.11.**

where (σ_f) is the flextural tensile strength of the tablet, (F) is the breaking load, (l) is the distance between the two lower rolls, (b) is the width of the tablet, (d) is the thickness of the tablet, (a) is the height of the curved segment and (A) is the area of the curved segment.

2.2.8. Hydration studies:

Hydration or “swelling” studies for all tablets used in this study were carried out using live in-situ image analysis. The settings for the hydration studies varied depending on the shape of the tablets used.

2.2.8.1. Hydration of round tablets:

2.2.8.1.1. Axial swelling studies:

The axial swelling of round tablets was monitored using an assembly consisting of a black and white camera (CCD-4 miniature video camera module, Rengo Co., Japan) with a zoom lens (18–108/2.5, Olympus Europe, Hamburg, Germany). The camera was connected to an image analyser (Seescan Solitaire 512, Seescan, Cambridge, UK). Three light sources were used to provide adequate illumination of the tablets. Two of these sources were placed at an angle of 45° on each side of the imaging stage (Highlight 3001, Olympus Optical Co. (Europe) GmbH, Hamburg, Germany). The third light source was placed on top of the stage (Halogen desk spotlight, Winsource Industries Ltd., Kln, Hong Kong).

The software was initially calibrated for length using a graduated ruler which was placed inside a glass beaker containing the same hydration medium used in the study to eliminate any influence arising from these factors. Round tablets were initially measured for height to 0.001 mm using a digital micrometer (Mitutoyo digital micrometer, Mitutoyo, Kawasaki, Japan). Each tablet was then individually placed on a specially assembled holder equipped with a set of pins (Figure 2.4.). This assembly was chosen to allow full surface hydration of the tablets. Each tablet was then placed in a glass beaker containing distilled de-aerated water at 37±1°C. The temperature of the hydration medium was maintained at 37°C by placing the beakers in a thermally controlled water bath (Unstirred water both, type JB6, Grants Instruments, Cambridge,

UK). At consecutive time intervals of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 255, 270, 285, 300, 315, 330, 345, 360, 375, 390, 405, 420, 435, 450, 465, and 480 minutes, each beaker was taken out, placed on the imaging stage, and black and white images of the tablet were taken and analysed manually for tablet overall height, which was defined as the distance between the two pole points for curved tablets, and between the two centre points of the axial faces of flat tablets. The swelling studies were carried out for 480 minutes.

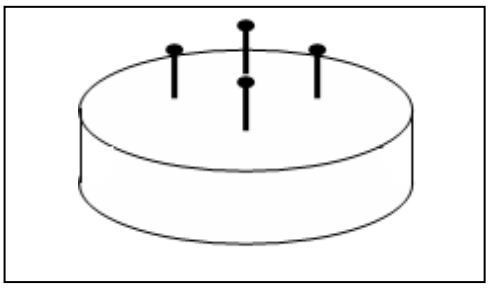

Figure 2.4. Shematic representation of the pin-holder assembly used in the swelling studies of round tablets.

The axial swelling indices of the hydrating tablets were calculated at the consecutive time intervals using equation 2.12.

$$SI_a = \left(\frac{height_t - height_0}{height_0} \right) \times 100\,\% \qquad \textbf{Equation 2.12.}$$

where (SI_a) is the tablet swelling index in the axial direction at time *t*, ($heigh_t$) and ($height_0$) are the heights of the tablet at time *t* and at the beginning of the experiment, respectively.

2.2.8.1.2. Radial swelling studies:

The radial swelling of round tablets was monitored using an assembly similar to that used in axial swelling studies with some modifications. Tablets were measured for diameter to 0.001 mm using a digital micrometer (Mitutoyo digital micrometer, Mitutoyo, Kawasaki, Japan), and then individually placed on the previously mentioned pin holders. Tablets were then placed inside a glass vessel containing distilled de-aerated water maintained at 37±1°C by means of a thermally controlled water bath (Tempette Junior TE-8J, S.H. Scientific, Blyth, UK). The black and white camera was placed on top of the hydration apparatus, together with two top light sources (Highlight 3001, Olympus Optical Co. (Europe) GmbH, Hamburg, Germany). The internal surface of the hydration vessel was coated with matt black adhesive paper to maximise the contrast between the tablets and their background. This was further enhanced by tuning the threshold level of the analysis software. A calibration step for the software was initially carried out using a graduated ruler placed inside the hydration vessel. Then, at consecutive time intervals, i.e. at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 255, 270, 285, 300, 315, 330, 345, 360, 375, 390, 405, 420, 435,

450, 465, and 480 minutes, black and white images of each tablet were taken and automatically analysed for tablet Feret diameter, which was defined as the mean of thirty six measurements of tablet diameter around the circumference. Swelling studies were carried out for 480 minutes.

The radial swelling indices of the hydrating tablets were calculated at consecutive time intervals using equation 2.13.

$$SI_r = \left(\frac{diameter_t - diameter_0}{diameter_0} \right) \times 100\% \qquad \textbf{Equation 2.13.}$$

where (SI_r) is the tablet swelling index in the radial direction at time *t*, ($diameter_t$) and ($diameter_0$) are the diameters of the tablet at time *t* and at the beginning of the experiment respectively.

2.2.8.2. Hydration of elongated tablets:

2.2.8.2.1. Height swelling studies:

For the investigation of the axial swelling of elongated tablets, certain modifications were made to the system used for the investigation of the swelling of round tablets. Initially three measurements for tablet width were performed (two at the two ends of the tablet and one at the centre of the tablet) to 0.001 mm using a digital micrometer (Mitutoyo digital micrometer, Mitutoyo, Kawasaki, Japan). The mean value of the three readings was used for further evaluation. In order to accommodate for the change in tablet shape and possible difference in swelling patterns, each

tablet was placed on a modified pin holder, where a piece of coated mesh was placed on top of the pins to maintain tablet integrity during hydration. Tablets were then individually placed in transparent glass boxes containing distilled de-aerated water at 37°C, and temperature control was achieved by placing the beakers in a thermally controlled water bath (Unstirred water both, type JB6, Grants Instruments, Cambridge, UK) maintained at 37±1°C.

At consecutive time intervals, i.e. at 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 255, 270, 285, 300, 315, 330, 345, 360, 375, 390, 405, 420, 435, 450, 465, and 480 minutes, each box was placed on the imaging stage, and tablet images were taken and manually analysed for tablet height. The mean of three measurements of tablet height, taken at the centre and both edges of the tablet, was used for tablet evaluation.

The Swelling indices for tablet height at the consecutive time intervals were calculated using equation 2.14.

$$SI_h = \left(\frac{height_{t-mean} - height_{0-mean}}{height_{0-mean}} \right) \times 100\% \qquad \textbf{Equation 2.14.}$$

where (SI_h) is the tablet height swelling index at time *t*, ($heigh_{t\text{-}mean}$) and ($height_{0\text{-}mean}$) are the mean values of tablet height at time *t* and at the beginning of the experiment, respectively.

2.2.8.2.2. Width and length swelling studies:

The width and length swelling of elongated tablets were investigated using an assembly similar to that used for round tablets. Tablets were initially measured for length to 0.01 mm using a digital calliper (UPM digital calliper, United Precision Machine Inc., Shenzhen, China), and for width to 0.001 mm using a digital micrometer (Mitutoyo digital micrometer, Mitutoyo, Kawasaki, Japan). Tablets were then placed individually into the hydration medium using the previously mentioned mesh holders. After calibration of the analysis software, the changes in tablet width and length were monitored at consecutive time intervals, i.e. at 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 255, 270, 285, 300, 315, 330, 345, 360, 375, 390, 405, 420, 435, 450, 465, and 480 minutes. For tablet length, one manual measurement was recorded from the image. For tablet width, the mean of three measurements, taken at the centre and at both ends of the tablet, was used for tablet evaluation, as illustrated in Figure 2.5.

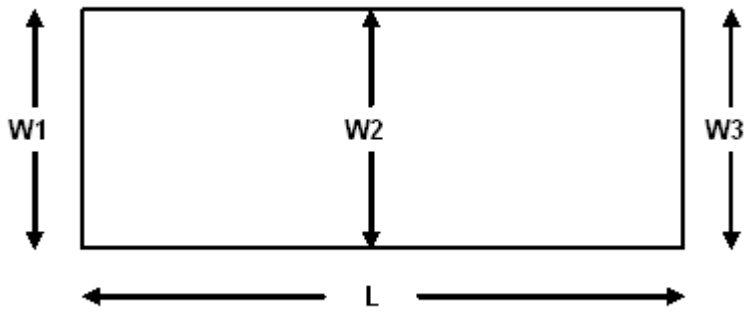

Figure 2.5. Schematic illustration of the radial measurements performed on hydrating elongated tablets, W: width, L: length.

The swelling indices for tablet width and length at consecutive time intervals were calculated using equations 2.15. and 2.16. respectively.

$$SI_w = \left(\frac{width_{t-mean} - width_{0-mean}}{width_{0-mean}} \right) \times 100\,\% \qquad \textbf{Equation 2.15.}$$

where (SI_w) is the tablet swelling index in the width direction at time *t*, ($width_{t\text{-}mean}$) and ($width_{0\text{-}mean}$) are the widths of the tablet at time *t* and at the beginning of the experiment respectively.

$$SI_l = \left(\frac{length_t - length_0}{length_0} \right) \times 100\,\% \qquad \textbf{Equation 2.16.}$$

where (SI_l) is the tablet swelling index in the length direction at time *t*, ($length_t$) and ($length_0$) are the lengths of the tablet at time *t* and at the beginning of the experiment respectively.

2.2.9. Characterisation of Xanthan Gum gel systems:

2.2.9.1. Preparation of gel samples:

Blank and drug containing Xanthan Gum gels were produced at three different concentrations of 2, 4 and 6% w/w. 25 grams of each gel was produced; initially, the weights of each formulation needed to make each

of the gel concentrations were calculated using equation 2.17., and are listed in Table 2.2.

$$W_{mix} = \frac{\left(C_g \times W_w\right)}{X_p}$$ **Equation 2.17**

where, (W_{mix}) is the weight of powder mix required, (C_g) is the required concentration of the gel, (W_w) is the weight of the aqeous powder dispersion used and (X_p) is the percentage fraction of the polymer in the powder mix. The percentage fraction of the polymer in each powder mix was based on the developed formulations, which is discussed in detail in Chapter 4.

Formulation	Gel Concentration (w/w %)		
	2%	4%	6%
A (Blank)	1.053	2.105	3.158
B (Orphenadrine Citrate)	1.429	2.857	4.286
C (Orphenadrine HCl)	1.429	2.857	4.286

Table 2.1. Weights of blank and drug containing Xanthan Gum mixtures, in grams, used for the preparation of gels used in the rheological studies.

Each accurately weighed sample was added to distilled de-aerated water at 37°C to obtain 25 grams of aqeous powder dispersion. The mixing was initially done using a magnetic stirrer equipped with a hot plate facility

which helped to maintain the gel temperature at 37°C. Stirring was carried out for 30 minutes. Gels that had a high viscosity hindered the movement of the stirrer after some time, thus stirring was continued manually using a glass rod. Gel storage was carried out at two stages. Initially, gels were placed in a thermally controlled water bath in sealed containers for 1 hour to enhance complete hydration, followed by storage at ambient conditions in air-tight amber glass containers for a further 24 hours to allow complete hydration.

2.2.9.2. Rheological studies:

All rheological studies were carried out using a controlled stress rheometer (Bohlin Gemini 200, Malvern Instruments Ltd., Malvern, UK), equipped with a parallel serrated plate geometry with a diameter of 25 mm, which was chosen to minimise gel sample slipping during measurements. The gap between the plates was set to 1 mm and all experiments were carried out at a constant temperature of 37°C. Gel samples were introduced between the plates and allowed to stand for 15 minutes to allow gel relaxation after sample handling, and to allow gel samples to equilibrate at the desired temperature. A solvent trap, and a plastic cover were used to enclose the plates and the sample, in order to maintain a humid atmosphere during measurements, and to prevent sample drying which could lead to the occurrence of artefacts. All rheological measurements were repeated three times using different samples.

2.2.9.2.1. Oscillation studies:

Dynamic oscillatory measurements were performed on each gel sample. Initially stress “amplitude” sweeps were done between 0.01 and 100 Pa at a constant frequency of 1 Hz to determine the linear viscoelastic region for each sample. Values of strain and corresponding stress from the middle part of the linear viscoelastic region were employed to carry out frequency sweeps between 0.01 and 20 Hz to investigate to relationship between the oscillation frequency and the rheological properties of the sample, i.e. elastic modulus, viscous modulus, and the phase angle.

2.2.9.2.2. Viscometric studies:

The flow behaviour of each gel sample was investigated in a controlled rate mode, using rates between 0.01 and 10 Hz. In order to investigate the presence of thixotropic behaviour in the gel samples, flow rate values were increased to the maximum of 10 Hz and then decreased once again to the minimum of 0.01 Hz in order to elucidate the presence and magnitude of the hysteresis loop associated with thixotropic behaviour.

In order to practically identify the yield stress of each gel sample studied, the rheometer was operated in the controlled stress mode, and the influence of changing the shear stress, between 0.1 and 100 Pa, on the values of gel strain and its instantaneous viscosity was monitored. The yield stress of each gel sample was automatically calculated depending on the deflection point observed in the curves.

2.2.10. Dissolution studies:

Preliminary studies indicated a significant absorbance exhibited by one of the excipients used in this study, which is Xanthan Gum. Thus it was necessary to construct calibration curves for all absorbing entities, i.e. the two drugs and Xanthan Gum. Two wavelengths were used for absorbance measurements using UV-spectrophotometry; 264 nm and 244 nm. The choice of wavelengths and calculations for obtaining the contribution of both; drug and polymer, in the overall absorbance at each wavelength, are discussed in detail in Chapter 7.

2.2.10.1. Construction of drug calibration curves:

In order to define the relationship between drug absorbance values and drug concentration, a calibration curve was constructed for each drug at the two wavelengths of 264 nm and 244 nm. A stock solution with a concentration of 1000 µg/ml was prepared volumetrically for each drug individually. Then drug solutions with concentrations of 5, 10, 20, 40, 60, 80, 100, 125, 150, 175, 200, 250, 300, 350, 400 and 450 µg/ml were prepared volumetrically using the stock solution. The absorbance of each solution was measured at both wavelengths of 264 nm and 244 nm using a double beam UV spectrophotometer (CE 594 Double Beam Spectrophotometer, Cecil Instruments, Cambridge, England). Two readings were recorded for each solution at each wavelength and the mean value was used for evaluation.

2.2.10.2. Construction of polymer calibration curves:

Due to the significant absorbance from the polymer, two calibration curves were constructed for the polymer at the two specified wavelengths. Accurately weight amounts of the polymer of 5, 10, 20, 40, 60, 80, 100, 125, 150, 175, 200, 250 and 300 mg were introduced individually into dissolution vessels of a paddle dissolution apparatus (Type DT6 R, Erweka Appartebau GmbH, Heusenstamm, Germany) containing 1000 ml of distilled de-aerated water each. Polymer dissolution was enhanced by applying a paddle rotation speed of 150 rpm. After six hours, samples where withdrawn from each dissolution vessel through filter tips with a pore size of 20 µm. The absorbance of each sample was recorded twice at the two wavelengths of 264 nm and 244 nm using a double beam UV spectrophotometer (CE 594 Double Beam Spectrophotometer, Cecil Instruments, Cambridge, England). Polymer calibration studies were repeated twice and the combined results of the two runs were used for further evaluation.

2.2.10.3. Tablet dissolution studies:

Tablet dissolution was carried out using the British Pharmacopeia paddle apparatus (Type DT6 R, Erweka Appartebau GmbH, Heusenstamm, Germany). Tablets were introduced individually into dissolution vessels containing 900 ml of distilled de-aerated water each, maintained at 37±1 °C. The paddle speed was set to 75 rpm. At specified time intervals of 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes,

10ml samples were withdrawn from each dissolution vessels through filter tips with a pore size of 20 μm. The absorbance of each sample was measured immediately at the two specified wavelengths of 264 nm and 244 nm using a double beam UV spectrophotometer (CE 594 Double Beam Spectrophotometer, Cecil Instruments, Cambridge, England).

For the dissolution studies of elongated tablets, a modification was introduced into the system. Tablets were individually placed on a purpose made sinker assembly (Figure 2.6.) in order to prevent the continuous collision between the tablets and the rotating paddles. Such an effect was caused by the nature of the size and shape of the tablets which caused the continuous rotation of the tablet immediately after insertion into the dissolution medium.

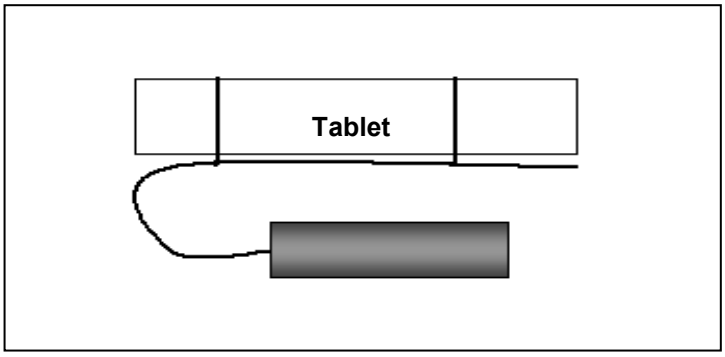

Figure 2.6. Schematic illustration of the metal sinkers used for dissolution studies of elongated tablets.

2.2.11. Scanning electron microscopy:

Scanning electron microscopy was used to get closer insight into the morphological and structural properties of the powders and tablets used in this study. All studies were carried out using the same scanning electron microscope (Hitachi S3000N Scanning Electron Microscope. Hitachi High-Tech Science Systems Corp., Japan)

2.2.11.1. Scanning electron microscopy of powder samples.

A small amount of each powders sample was dispersed on the surface of a double sided adhesive black paper, which was mounted on a small round metal stub. The samples were subjected to a brief air jet to remove any agglomeration of the powder. The powder samples were initially coated with a thin layer of gold palladium sputter (Polaron SC7620, Quoron Technologies, Newhaven, UK), and then introduced into the imaging chamber of the scanning electron microscope. The microscope was operated at a voltage of 5kV, and microscopic images of the powder were acquired at various magnification powers.

2.2.11.2. Scanning electron microscopy of tablets.

Two main features of the tablets were investigated using scanning electron microscopy, i.e. tablet surface and the fracture surface of the tablets after being subjected to diametral compression. Whole tablets were used for surface imaging and fractured tablets were used for

fracture surface imaging. The tablets were mounted on double sided black adhesive paper on round metal stubs, coated with a thin layer of gold palladium sputter (Polaron SC7620, Quoron Technologies, Newhaven, UK), and then introduced into the imaging chamber of the scanning electron microscope. The microscope was operated at a voltage of 20kV and tablet surfaces and fracture surfaces were imaged at various magnification powers.

2.2.11.3. Scanning electron microscopy of hydrated tablets.

For the microscopic imaging of the surface properties of hydrated tablets, tablets were initially allowed to hydrate adequately by placing them in a glass beaker containing distilled de-aerated water maintained at 37±1 °C by means of a thermally controlled water bath (Unstirred water both, type JB6, Grants Instruments, Cambridge, UK). Prior to imaging, tablets were removed from the hydration medium and wiped gently with an absorbing tissue to remove excess water from the surface. Each tablet was then placed on a round metal stub and placed on a cooling stage within the imaging chamber of the scanning electron microscope. The temperature of the cooling stage and the pressure within the imaging chamber were adjusted to keep the tablet at a stage very close to freezing without allowing ice formation, a special sample holder was used to maintain the sample at low temperatures (XVP Coolstage, Deben UK Ltd, Suffolk, UK). Images of the hydrated tablet surface were acquired at various magnification powers.

2.2.12. Thermal investigation of powders and dried gel samples:

2.2.12.1. Preparation of dried gel samples:

Gel samples were prepared at concentrations of 2, 4 and 6% w/w. Gels contained either pure Xanthan Gum or binary mixtures of Xanthan Gum and either of the two model drugs used in the study. The Xanthan Gum to drug ratio in drug containing mixtures was kept equivalent to their ratio in the formulations used elsewhere in the study.

The use of binary polymer-drug mixtures instead of whole formulations was chosen to elucidate any potential interactions between the polymer and either of the two drugs.

Gel preparation was carried out using a process identical to that described in section 2.2.9.1. The weights of pure Xanthan Gum powder and binary Xanthan Gum-drug mixtures used in the preparation of the various gels are listed in Table 2.2.

Powder Mixture	Gel Concentration (w/w %)		
	2%	4%	6%
Blank Xanthan Gum	0.500	1.000	1.500
Xanthan Gum + Orphenadrine Citrate	0.857	1.714	2.572
Xanthan Gum + Orphenadrine HCl	0.857	1.714	2.572

Table 2.2. Weights of pure and drug containing Xanthan Gum mixtures, in grams, used for the preparation of gels investigated by the thermal studies.

After 24 hours, gel samples were placed on flat trays and dried for three hours at 50°C, then stored in a silica gel desiccator for 7 days to complete the dehydration process prior to use.

2.2.1.2.1. Thermal investigation:

Thermal investigation of the powder and gel samples used in this study was carried out to further elucidate the physicochemical nature of these systems. All thermal studies were carried out using differential scanning calorimetery, employing a temperature modulated differential scanning calorimeter (TA Q1000, TA Instruments Ltd, Crawly, UK). Prior to use, the temperature modulated differential scanning calorimeter was calibrated for enthalpy using Indium and for heat capacity using sapphire.

For the thermal investigation of the powder and dried gel samples, samples of 4-5mg were initially encapsulated in crimped Aluminium pans. The pans were introduced into the heating chamber of the differential scanning calorimeter, which was operated in the modulated mode, using Nitrogen as a purge gas at a flow rate of 50ml/min. Sample heating was carried out between 10°C and 230°C at a heating rate of 3°C/min. Temperature modulation during the heating cycle included an oscillation amplitude of 0.5 °C, and an oscillation period of 50 seconds.

2.2.13. Statistical analysis:

Statistical analysis of the data used in this study was carried out using two available software packages; SPSS® 14.0 for Windows® (SPSS release 14.0.0. SPSS Inc., Chicago, USA), and Microsoft Excel for Microsoft Office XP® (Microsoft Office XP®, professional edition, Microsoft Corp., Washington, USA).

CHAPTER THREE

3. Choice and characterisation of pharmaceutical materials

3.1. Introduction:

As has been discussed previously in chapter one, the physicochemical properties of the materials used in the formulation of hydrophilic matrix tablets have a major effect on the physical properties of the produced tablets and on their hydration behaviour. It was thus important to choose the appropriate pharmaceutical materials, which would help in fulfilling the main aims of this study. It was also important to thoroughly characterise the physicochemical properties of all materials used. Hence, the main aims of this part of the study were to choose the appropriate materials and to characterise the main physicochemical properties associated with them. This in turn could give further insight into the physical and hydration behaviour of the produced tablets.

Another important aim, associated with this chapter, is attributed to the nature of some of the excipients used in this work. A material such as

spray dried lactose could exist in different polymorphic forms. Such variation, as will be discussed in this chapter, could have a significant influence on the properties of the produced tablets, and thus introduce undesired variables that may hinder the investigation of the main focus points of this study, which are the influence of tablet shape properties, and drug physicochemical properties. It was hence important to characterise such properties and monitor them throughout the span of the study.

3.2. Choice of Materials:

3.2.1 Choice of polymer:

The choice of the hydrophilic polymer used in this study, was done in accordance with one of the main aims of this study, which is the investigation of the possible ionic interaction between the matrix forming polymer and the drug incorporated into the formulation. Xanthan Gum, as was previously discussed, is an anionic polymer that has the potential of interacting with oppositely charged cationic drugs. Moreover, Xanthan Gum has an advantageous property, which is its ability to rapidly forming gel-like structures with high viscosities, even at low concentrations.

3.2.2. Choice of model drugs:

Two main factors influenced the choice of the two model drugs used in this study. The first of which is directly related to the potential for ionic interaction between the drug and the hydrophilic polymer. A cationic drug

was required to introduce the possibility of interaction with the anionic Xanthan Gum. The other factor was drug solubility. Two drugs were required, with similar chemical structure but varying in solubility. The two cationic drugs, Orphenadrine Citrate and Orphenadrine Hydrochloride were thus chosen. The first is freely soluble in water with an aqueous solubility of 1 part in 1 part of water, whereas the latter is sparingly soluble in water with an aqueous solubility of 1 part in 70 parts of water. Thus, the influence of drug solubility on the hydration process and on the potential ionic interaction could be studied.

The other excipients used in the study were chosen to facilitate the process of tablet production. Spray dried lactose and Emcompress® were used as diluents and magnesium stearate was used as a lubricant incorporated into the formulation.

3.3. Results and discussion:

3.3.1. Characterisation of particle size and morphological properties:

The particle size of the active ingredients and excipients incorporated into hydrophilic matrix tablets is considered a major factor influencing the overall behaviour of the tablets (Tros de llarduya et al 1997, Sumathi et al 2003, Dhopenshwarkar and Zats 1993).

A combined microscopic technique was adopted in the characterisation of the particle size and morphological properties for all powders used in this

study. Light microscopy accompanied with automatic image analysis was used to characterise the particle size distribution of the powders. Three measured parameters were used to characterise the size of each particle, i.e. the particle projected area, its minimum Feret diameter and its maximum Feret diameter. One further parameter, the McCarthy elongation (McCarthy 1976) was used to characterise the two-dimensional shape properties of the particles.

$$\text{McCarthy Elongation} = \frac{\text{Particle Feret diameter in the direction it is maximum.}}{\text{Particle Feret diameter in the direction it is minimum.}}$$

Equation 3.1. McCarthy elongation (McCarthy, 1976).

In conjunction with light microscopy, scanning electron microscopy was used to give a more detailed characterisation of the three-dimensional morphological properties of all powders.

3.3.1.1. Orphenadrine Citrate:

Size parameters for Orphenadrine Citrate Powder are shown below (Table 3.1.). The values indicate a powder with a rather fine particle size with median values of 19 μm for the maximum Feret diameter, 11 μm for the minimum Feret diameter and 125 μm^2 for particle projected area.

Parameter	Lower Quartile (25%)	Median (50%)	Upper Quartile (75%)	Mode
Maximum Feret diameter (μm)	10	19	37	6
Minimum Feret diameter (μm)	6	11	22	3
Area (μm^2)	35	125	450	8
McCarthy Elongation	1.43	1.67	2.00	1.81

Table 3.1. Particle size parameters for Orphenadrine Citrate powder.

The cumulative undersize frequency curves for the minimum and maximum Feret diameters (Figure 3.1.) also indicate a rather narrow particle size distribution composed mainly of fine particles with a lower percentage of larger particles, which is reflected in the low mode values for each of the parameters.

The two dimensional shape properties of the particles, in the form of the McCarthy elongation (Table 3.1.) and (Figure 3.2.) indicate the abundance of elongated particles in the powder system. This fact is made clearer in the SEM images (Figures 3.3. and 3.4.) which show the presence of large amounts of elongated rectangular shaped particles.

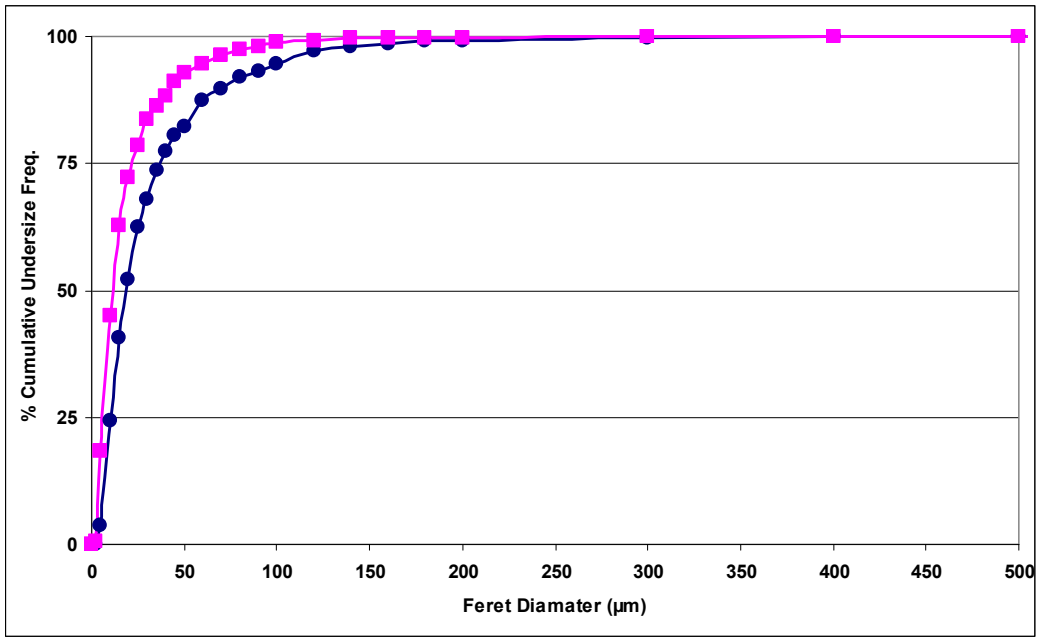

Figure 3.1. Percentage cumulative undersize frequency curve for Orphenadrine Citrate powder, -■- minimum Feret diameter, -●-maximum Feret diameter.

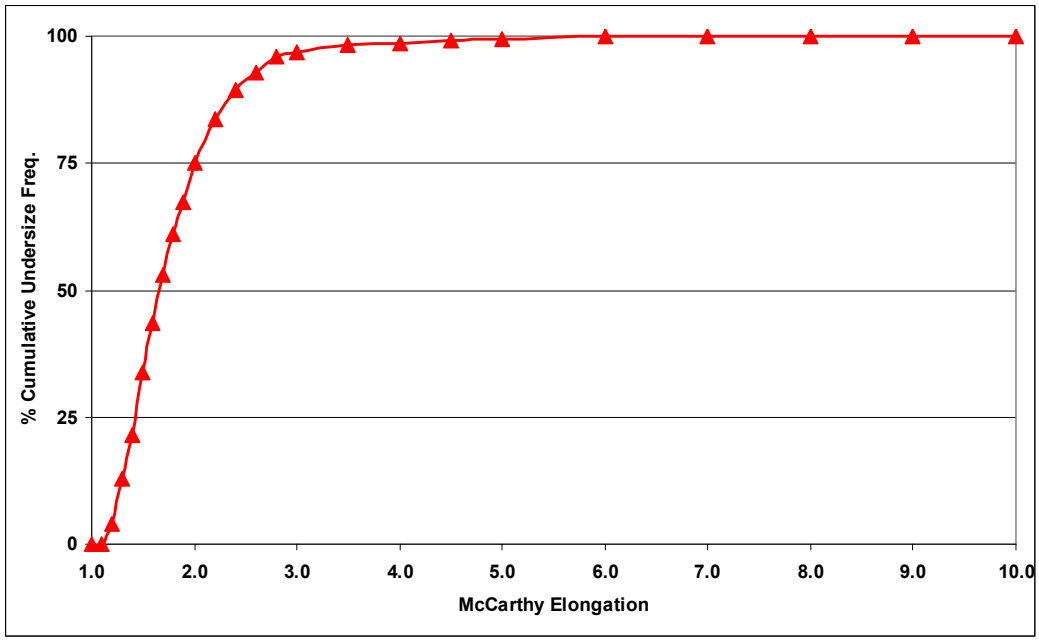

Figure 3.2. Percentage cumulative undersize frequency curve of McCarthy elongation for Orphenadrine Citrate powder.

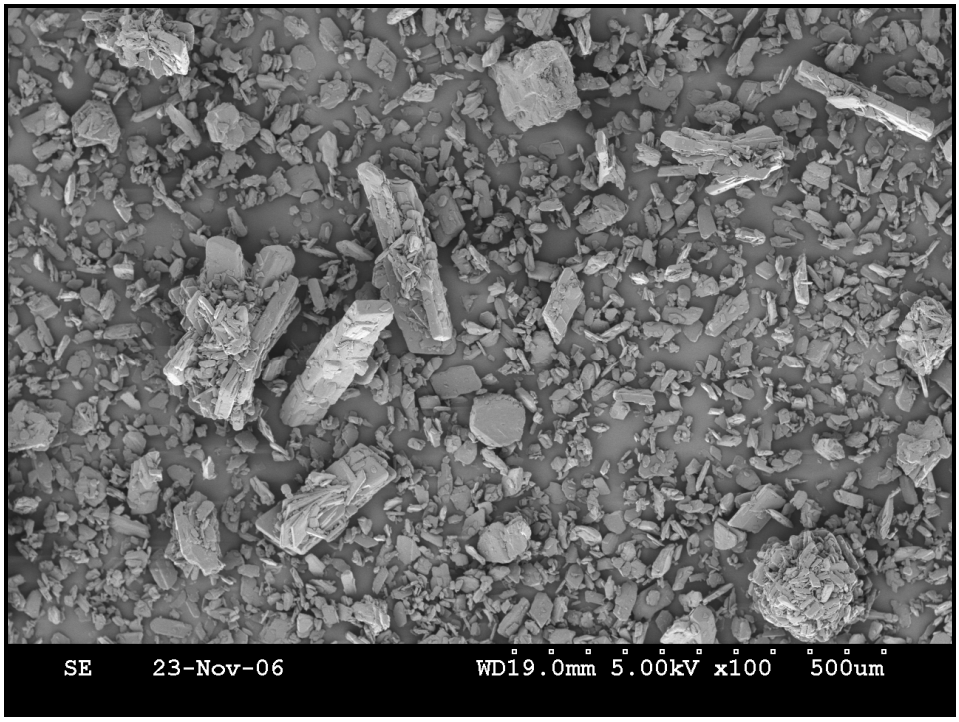

Figure 3.3. SEM image of Orphenadrine Citrate powder (magn. 100x).

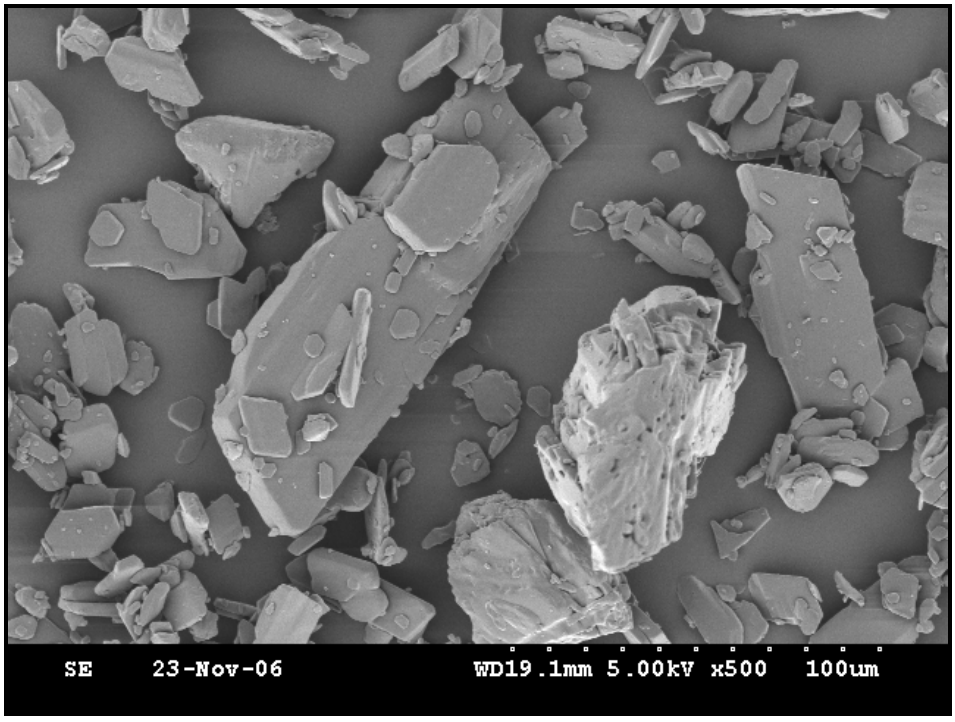

Figure 3.4. SEM image of Orphenadrine Citrate powder (magn. 500x).

3.3.1.2. Orphenadrine Hydrochloride:

Size parameters associated with the drug Orphenadrine HCl (Table 3.2.) and (Figure 3.5.), indicate an even finer powder in comparison with Orphenadrine Citrate. The HCl form has median values of 4 μm, 6 μm, and 10 μm^2 for the minimum Feret diameter, maximum Feret Diameter and projected area, respectively.

Parameter	Lower Quartile (25%)	Median (50%)	Upper Quartile (75%)	Mode
Maximum Feret diameter (μm)	3	6	10	3
Minimum Feret diameter (μm)	2	4	6	2
Area (μm^2)	5	10	35	2
McCarthy Elongation	1.38	1.60	1.93	1.80

Table 3.2. Particle size parameters for Orphenadrine HCl powder.

The cumulative undersize frequency curves for the minimum and maximum Feret values (Figure 3.5.) also indicate a much narrower particle size distribution as compared to Orphenadrine Citrate. In terms of the shape properties, no great difference is observed between the values obtained for Orphenadrine HCl (Table 3.2.) and (Figure 3.6.) and those obtained for Orphenadrine Citrate. This finding is supported by the SEM images obtained for Orphenadrine HCl (Figures 3.7. and 3.8.) which show the abundance of elongated particles in the powder system. However, the sizes of the particles are smaller than those of Orphenadrine Citrate.

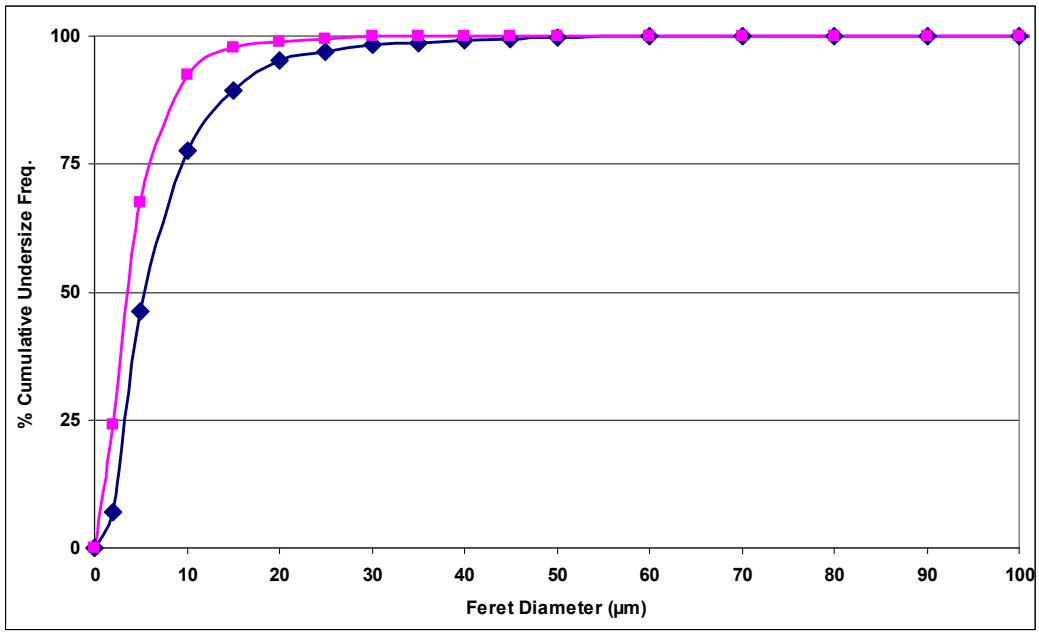

Figure 3.5. Percentage cumulative undersize frequency curve for Orphenadrine HCl powder, -■- minimum Feret diameter, -●-maximum Feret diameter.

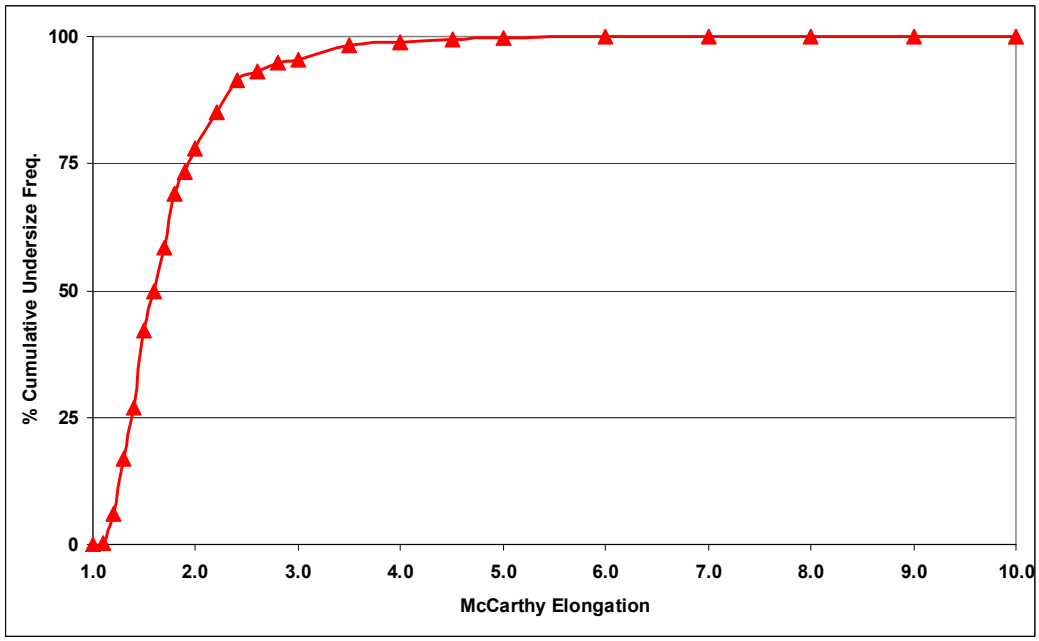

Figure 3.6. Percentage cumulative undersize frequency curve of McCarthy elongation for Orphenadrine HCl powder.

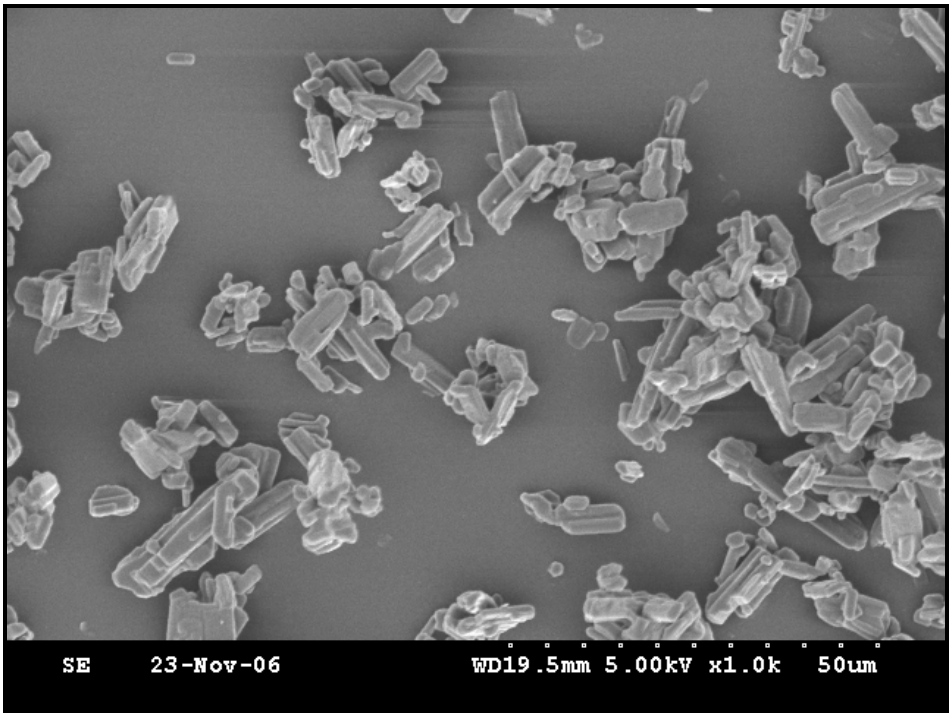

Figure 3.7. SEM image of Orphenadrine HCl powder (magn. 1000x).

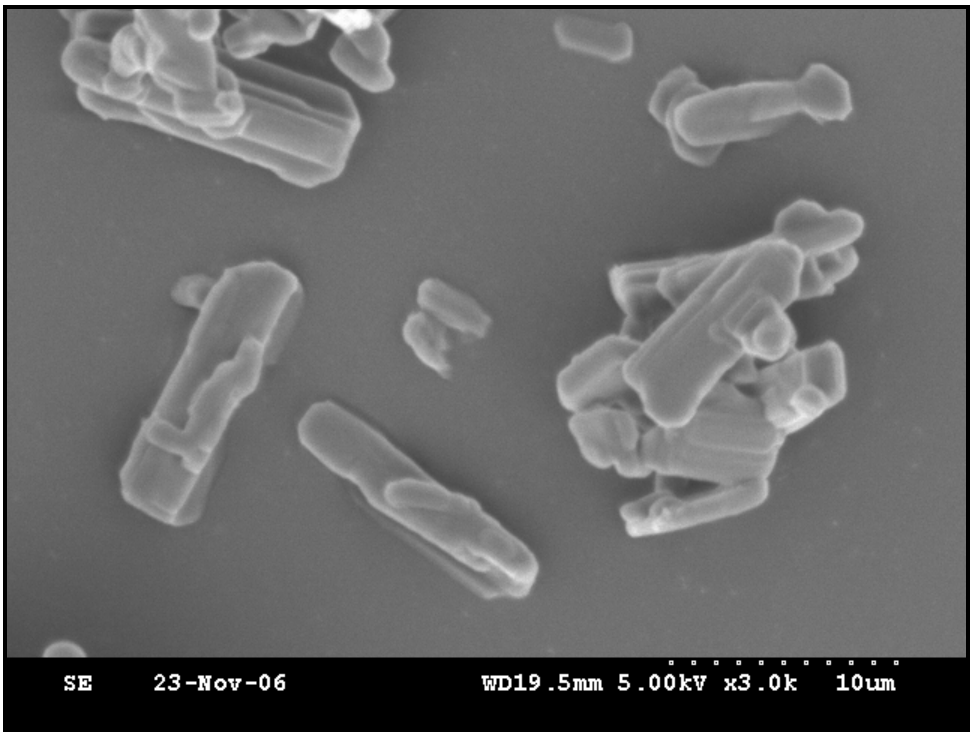

Figure 3.8. SEM image of Orphenadrine HCl powder (magn. 3000x).

3.3.1.3. Xanthan Gum:

Xanthan Gum is a microbiologically produced polymer, which is available in a number of size ranges (Singh 2006). The crucial role of the polymer in the mechanism of action of hydrophilic matrix systems, and the previously discussed influence of polymer particle size on this mechanism of action, makes it essential to give a thorough characterisation of the size and shape properties associated with this polymer.

The size parameters and size distribution of Xanthan Gum powder (Table 3.3) and (Figure 3.9.) indicate a powder with a large percentage of fine particles, with median values of 13 μm, 29 μm, and 190 μm^2 for the minimum Feret diameter, maximum Feret diameter, and projected area, respectively. This is also supported by the low mode values associated with all three parameters. However, further observation of Figure 3.9. indicates the presence of wider size distribution as compared to the previous materials, with the presence of a certain percentage of large particles.

In terms of shape properties, the two-dimensional results obtained for the McCarthy elongation for Xanthan Gum powder (Table 3.3) and (Figure 3.10.), indicate the presence of particles with a higher degree of elongation, with a median value of 2.07. Furthermore, the percentage cumulative undersize curve for this parameter (Figure 3.10.) shows a clear shift towards higher values as compared to those obtained for the other materials used in the study.

Further investigation of the morphological characteristics of Xanthan Gum powder system using SEM, (Figures 3.11. and 3.12.), revealed the presence of angular shaped particles in addition to some fibrous particles that are heavily elongated.

Parameter	Lower Quartile (25%)	Median (50%)	Upper Quartile (75%)	Mode
Maximum Feret diameter (μm)	18	29	48	9
Minimum Feret diameter (μm)	8	13	24	7
Area (μm^2)	80	190	640	38
McCarthy Elongation	1.57	2.07	2.82	2.69

Table 3.3. Particle size parameters for Xanthan Gum powder.

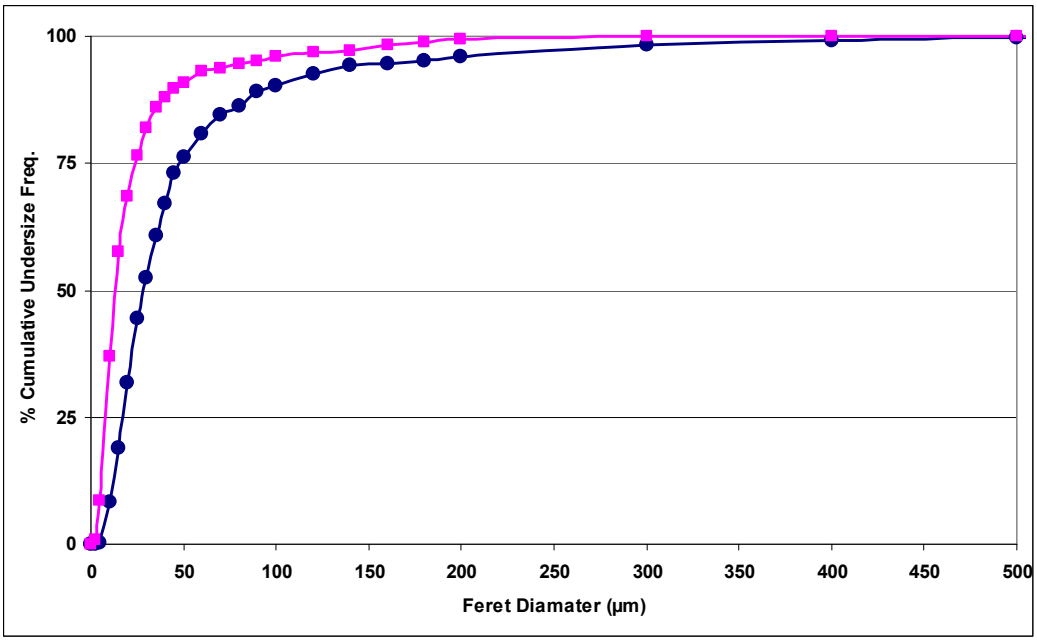

Figure 3.9. Percentage cumulative undersize frequency curve for Xanthan Gum powder, -■- minimum Feret diameter, -●-maximum Feret diameter.

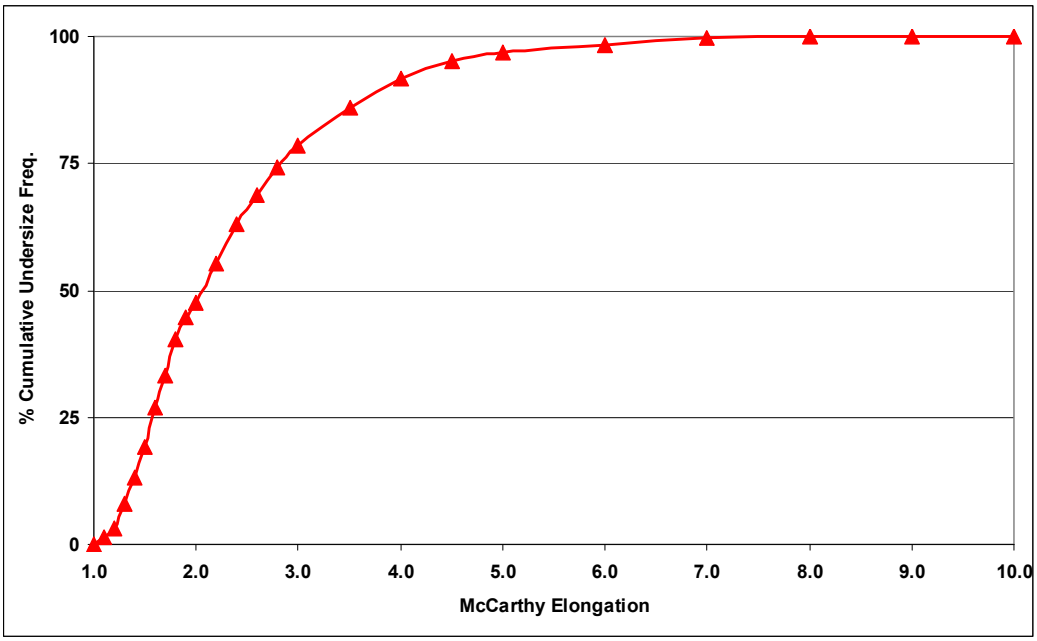

Figure 3.10. Percentage cumulative undersize frequency curve of McCarthy elongation for Xanthan Gum powder.

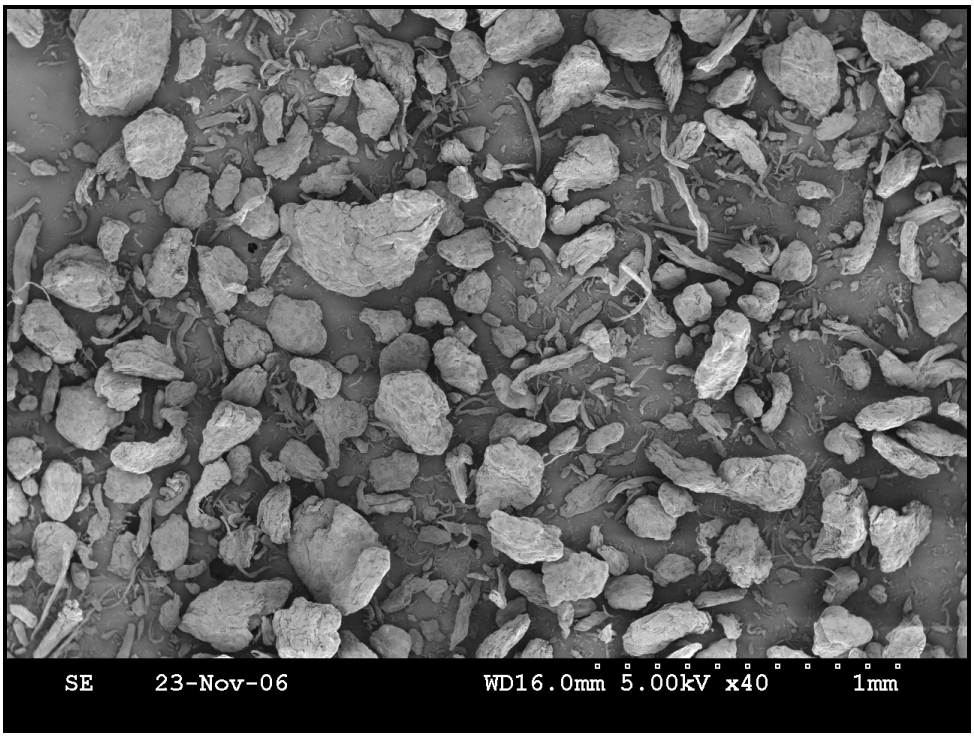

Figure 3.11. SEM image of Xanthan Gum powder (magn. 40x).

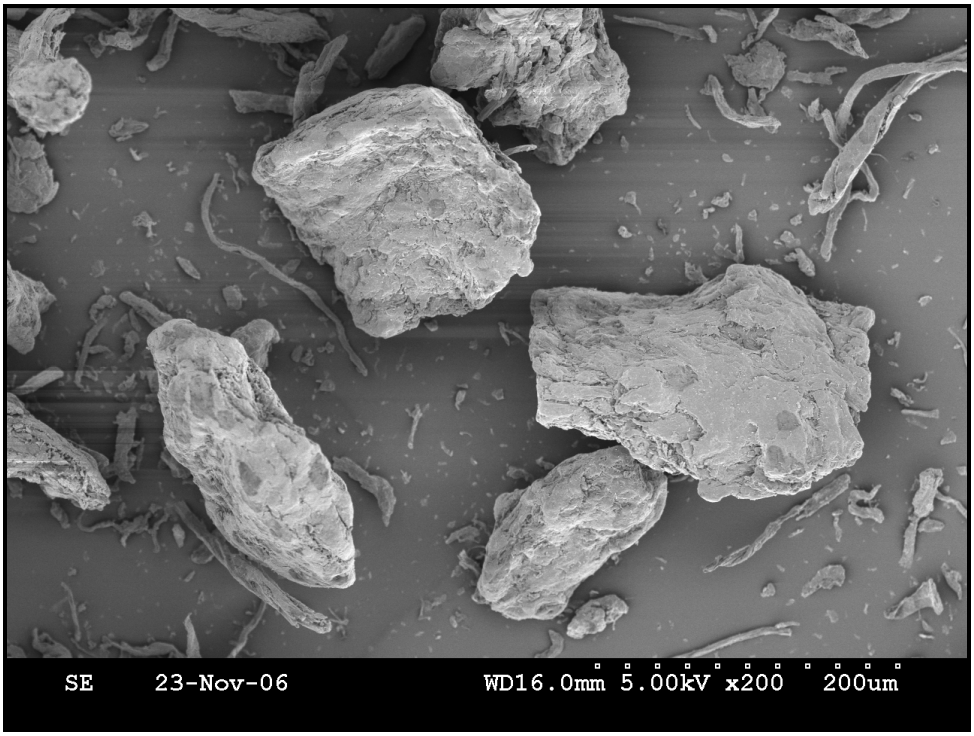

Figure 3.12. SEM image of Xanthan Gum powder (magn. 200x).

3.3.1.4. Spray Dried Lactose:

As will be discussed later, spray dried lactose is the main diluent used in the formulation of tablets investigated in this study. Moreover, this diluent has a high aqueous solubility. It is thus important to have a clear understanding of the particle size and shape properties of this material, as they could have a significant influence on the compaction and hydration behaviour of the tablets, and on the process of drug release.

The size parameters of spray dried lactose are presented below (Table 3.4.) and (Figure 3.13.). The average particle size of the spray dried lactose batch used in this study is comparable to those reported elsewhere in literature where 40-60% of particles had a particle size of

less than 100 μm (Kibbe 2000). Further investigation of the size distribution of this batch reveals a rather wide particle size distribution with a high percentage of fines as well as large particles. This feature could in turn be attributed to the nature of spray dried lactose. It is composed of aggregates of α-lactose monohydrate produced by spray drying (Hutton et al 1972). Spray dried lactose aggregates could have various sizes and they could also fragment into smaller particles during the preparation of the microscopy slide giving rise to a wide particle size distribution.

Parameter	Lower Quartile (25%)	Median (50%)	Upper Quartile (75%)	Mode
Maximum Feret diameter (μm)	17	60	130	16
Minimum Feret diameter (μm)	9	38	93	5
Area (μm^2)	80	1160	7660	7
McCarthy Elongation	1.31	1.54	1.96	1.81

Table 3.4. Particle size parameters for spray dried lactose powder.

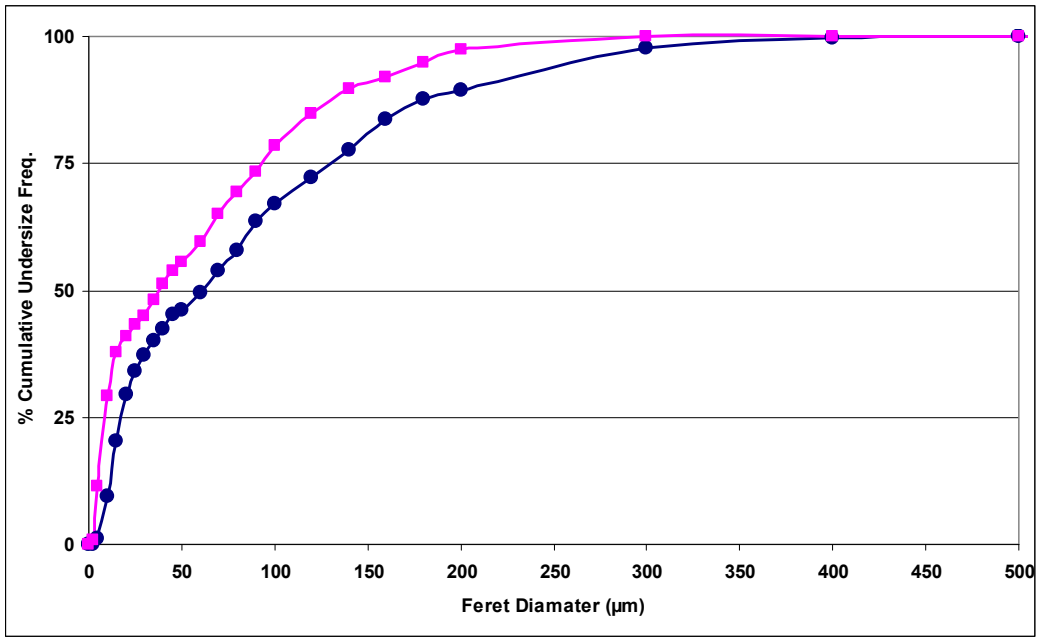

Figure 3.13. Percentage cumulative undersize frequency curve for Spray Dried Lactose powder, -■- minimum Feret diameter, -●-maximum Feret diameter.

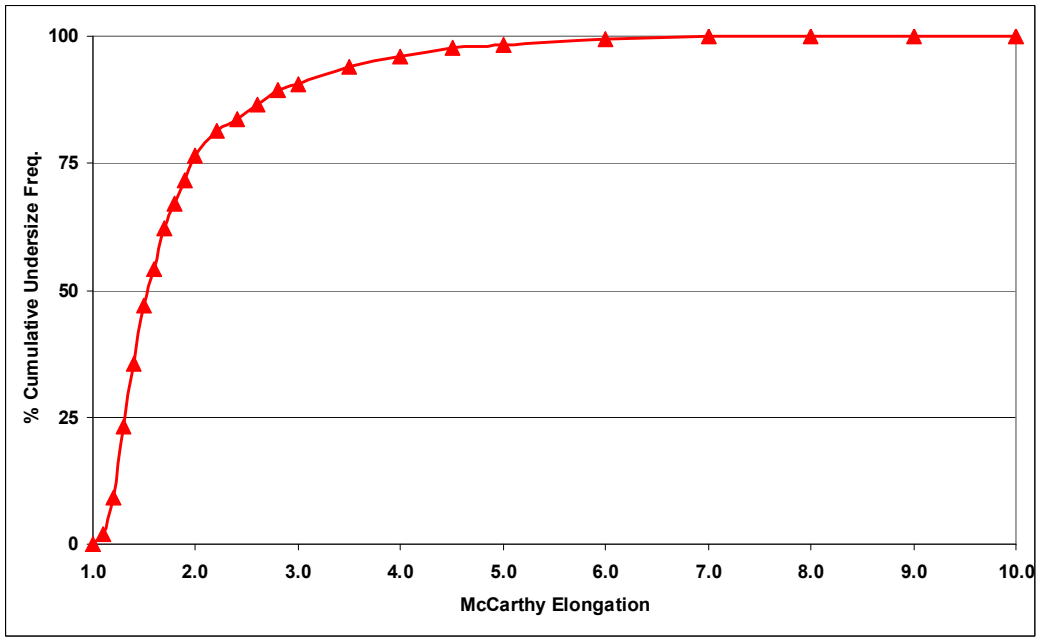

Figure 3.14. Percentage cumulative undersize frequency curve of McCarthy elongation for spray dried lactose powder.

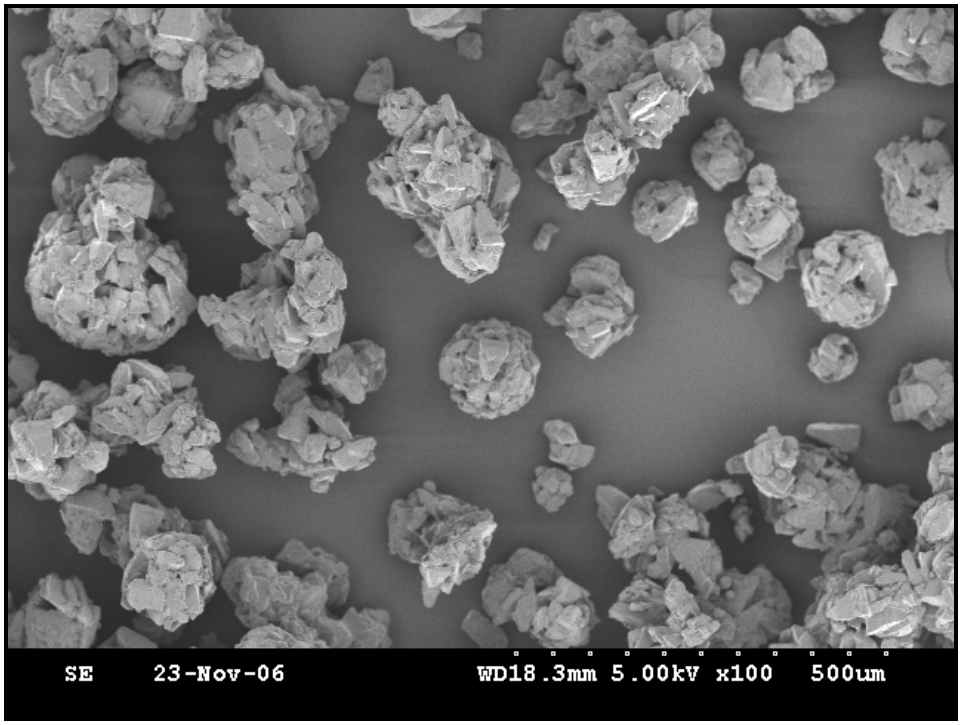

Figure 3.15. SEM image of spray dried lactose powder (magn. 100x).

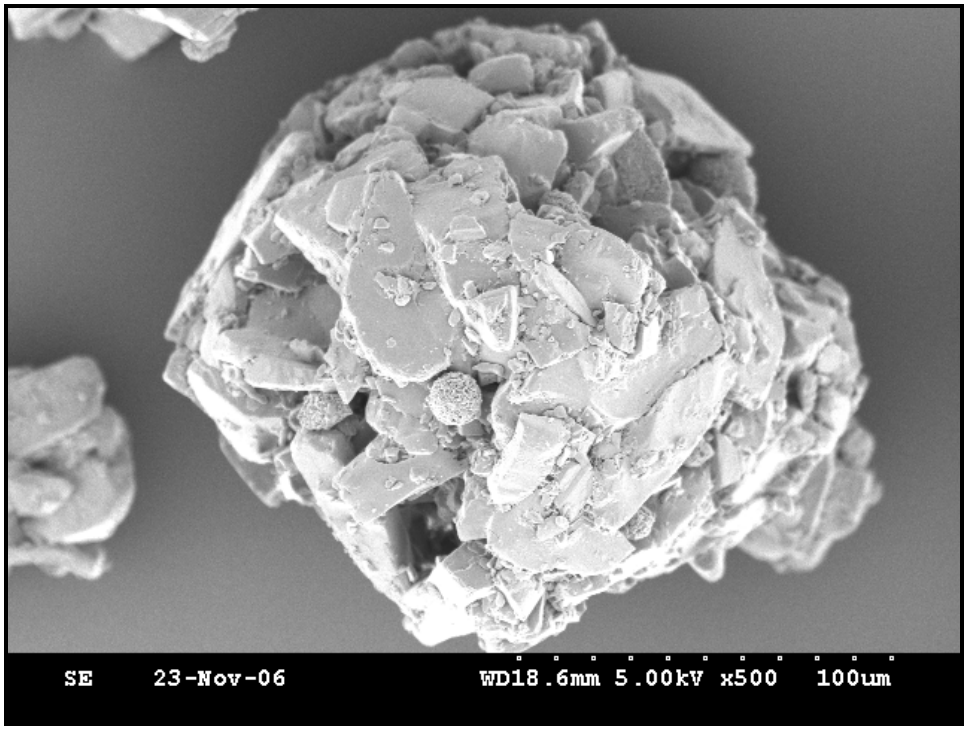

Figure 3.16. SEM image of spray dried lactose powder (magn. 500x).

The two-dimensional shape properties of spray dried lactose, (Table 3.4.) and (Figure. 3.14.) indicate the presence of some degree of elongation. The median value of McCarthy elongation is 1.54. However, in comparison to Xanthan Gum, the distribution of this elongation value associated with spray dried lactose (Figure. 3.14.) appears to be narrower. Such findings are further elucidated by the SEM images obtained for spray dried lactose (Figures 3.15. and 3.16.), which show the presence of rather spherical aggregated particles with some degree of elongation. Elongated crystal shaped smaller particles are also present.

3.3.1.5. Dibasic Calcium Phosphate Dihydrate (Emcompress ®):

Particle size parameters and size distribution of Emcompress® powder are presented below (Table 3.5) and (Figure 3.17.), respectively. The low median values of particles size parameters, 13 µm, 24 µm, and 145 μm^2 for the minimum Feret diameter, maximum Feret diameter and area, respectively could be attributed to the presence of a large amount of

Parameter	Lower Quartile (25%)	Median (50%)	Upper Quartile (75%)	Mode
Maximum Feret diameter (µm)	13	24	101	13
Minimum Feret diameter (µm)	6	13	63	5
Area (μm^2)	45	145	4020	7
McCarthy Elongation	1.42	1.70	2.27	1.42

Table 3.5. Particle size parameters for Emcompress® powder.

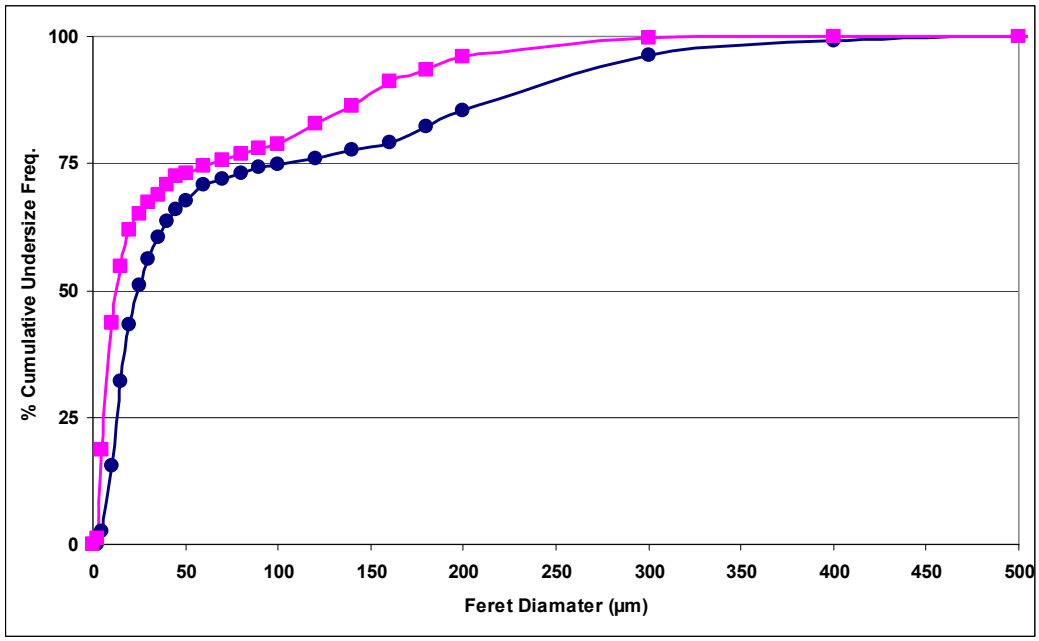

Figure 3.17. Percentage cumulative undersize frequency curve for Emcompress® powder, -■- minimum Feret diameter, -●-maximum Feret diameter.

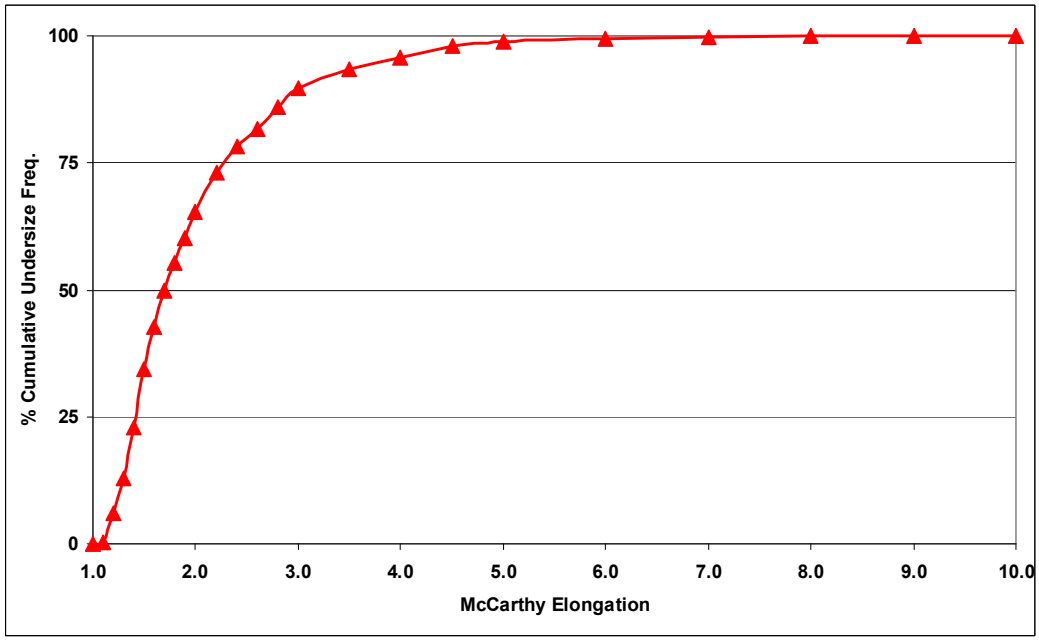

Figure 3.18. Percentage cumulative undersize frequency curve of McCarthy elongation for Emcompress® powder.

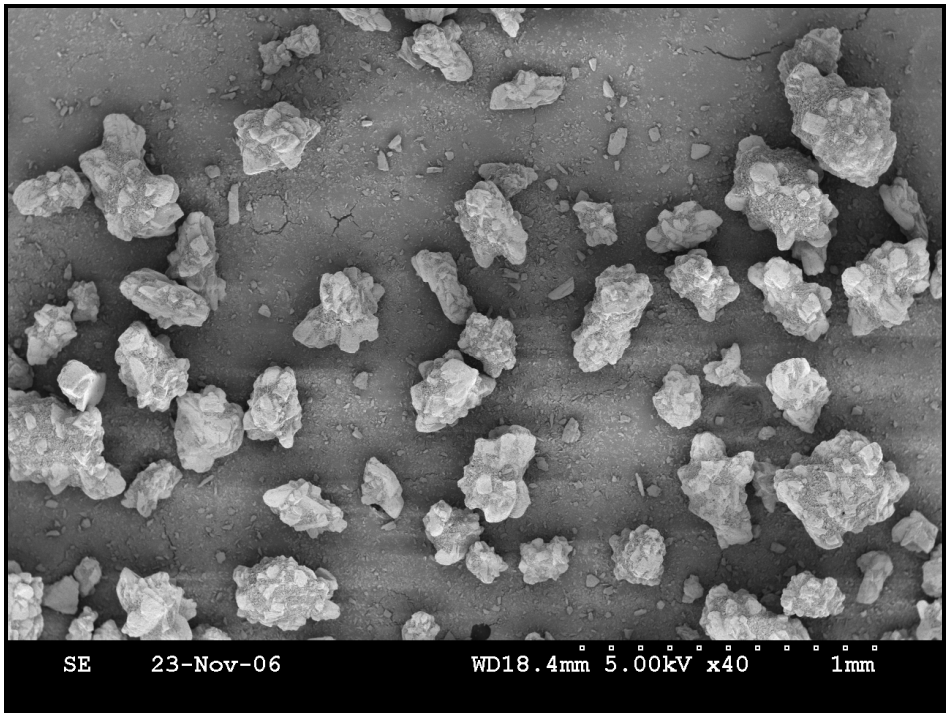

Figure 3.19. SEM image of Emcompress® powder (magn. 40x).

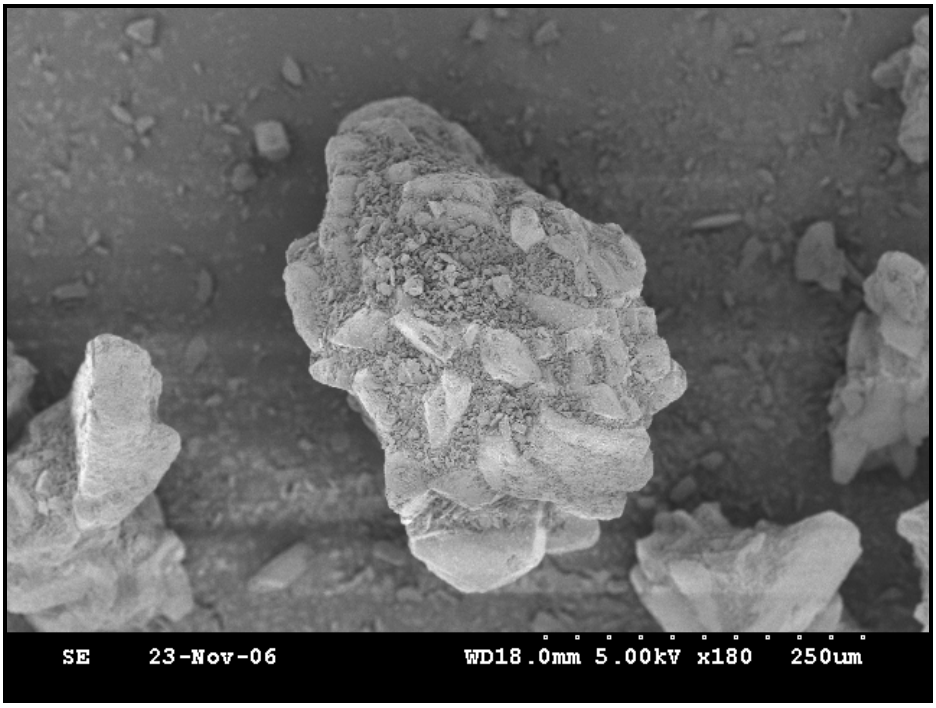

Figure 3.20. SEM image of Emcompress® powder (magn. 180x).

fine particles in the powder system. However, further investigation shows the presence of a wide particle size distribution (Figure 3.17). This is further supported by the considerable gap between the median values of all parameters and their upper quartile values (Table 3.5.). Such behaviour could originate from the fragmentation of the larger brittle Emcompress® particles into multiple smaller ones, giving rise to a system containing large fractions of coarse and fine particles.

In terms of shape properties, the values of McCarthy elongation associated with Emcompress® powder indicate the presence of particles with some degree of elongation. The value distribution curve (Figure 3.18) indicates a wider value distribution as compared to spray dried lactose. SEM images (Figures 3.19. and 3.20.) give more clarity to this, as they illustrate the presence of coarse and fine particles of varying degrees of elongation in the system.

3.3.1.6. Magnesium Stearate:

Magnesium Stearate is a lubricant used in the production of pharmaceutical tablets. It has a very low particle size, hence it was not possible to use light microscopy to produce reliable particle size distribution measurements for this powder. SEM images of the powder (Figures 3.21 and 3.22.) revealed a range of fine crystal aggregates of varying sizes.

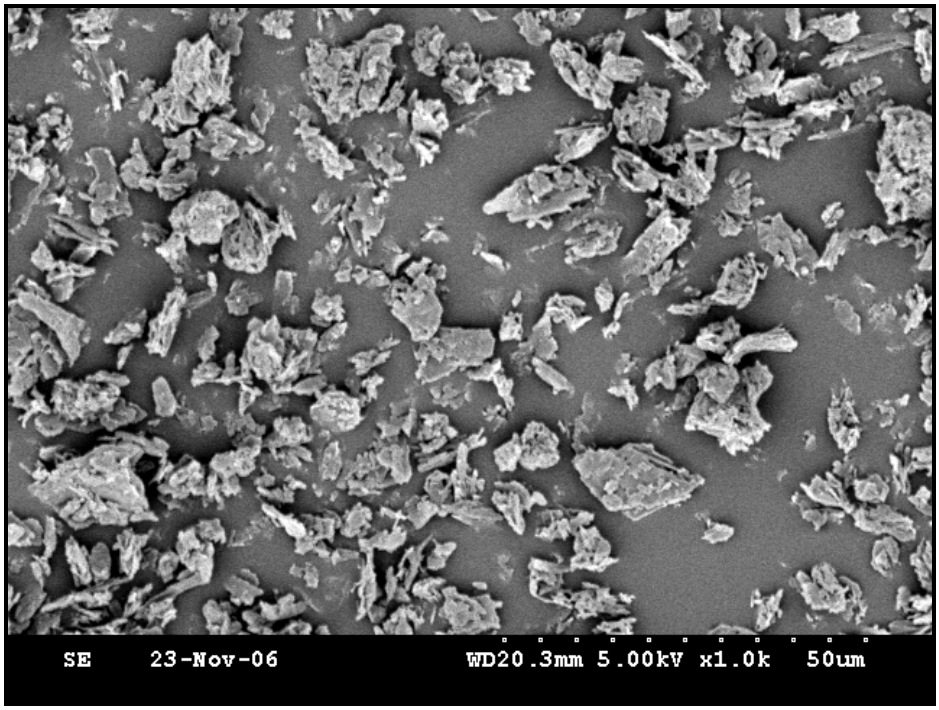

Figure 3.21. SEM image of magnesium stearate powder (magn. 1000x).

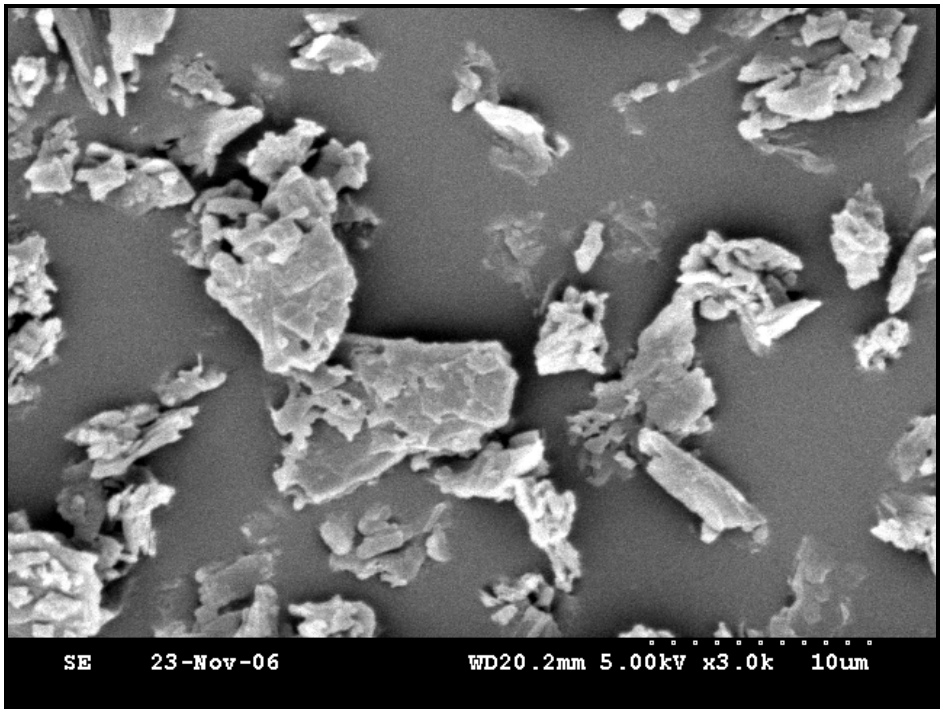

Figure 3.22. SEM image of magnesium stearate powder (magn. 3000 x).

3.3.2. Determination of the moisture content of the powders:

The moisture content of pharmaceutical powders may have a significant influence on the compaction properties of the powders, and by that influencing the physical properties and behaviour of the produced tablets.

The moisture contents of the drug and excipient powder systems used in this study were determined using halogen moisture analysis. The results are presented in Table 3.6. Sample heating was carried out at 90°C for all samples apart from magnesium stearate which undergoes a melting process above 50°C, thus the heating for this material was carried out at 50°C The two drugs, Orphenadrine Citrate and Orphenadine HCl, contained minimal amount of moisture content with equal values of 0.1%. As for the excipients, Xanthan Gum contained the highest moisture content of 12.46% and this is in accordance with a previously reported reference value of ≤ 15% (Singh 2006). This behaviour could be attributed to the hydrophilic property of the polymer. The other excipients exhibited lower and varying degrees of moisture content. The values for spray dried lactose and magnesium stearate were in accordance with reference values of ≤ 0.5% (Edge et al 2006), and ≤ 6% (Allen and Luner 2006), respectively.

As for Emcompress®, the measured value of 2.23% was considerably lower than the reference value reported in literature of 19.5-22% (Moreton 2006). One explanation for this could lie in the particle size properties associated with this powder. The presence of a large amount of fine

particles in the powder system used in the study may have facilitated the process of moisture loss, due to the much greater surface area available in smaller particles.

Powder	Moisture Content (%)	Heating temperature (°C)
Orphenadrine Citrate	0.10	90
Orphenadrine Hydrochloride	0.10	90
Xanthan Gum	12.46	90
Spray Dried Lactose	0.11	90
Dibasic Calcium Phosphate Dihydrate (Emcompress ®)	2.23	90
Magnesium Stearate	1.03	50

Table 3.6. Percentage moisture content of drug and excipient powders.

3.3.3. Determination of the apparent densities of the powders:

Determination of the apparent densities of all powders incorporated into the formulations used in this study was done using helium pycnometry. This is a rather non-destructive technique for obtaining the apparent density of pharmaceutical powders.

This technique provides the closest measurements of the true volume of a material as it depends on the advantageous properties of helium molecules which are able to penetrate pores and surface structures as small as one Ångstrom, due to their small size.

Initially the apparent densities of all powders in their ambient state were determined. However, certain materials, such as hydrophilic polymers, may adsorb large amounts of moisture on their surface. This may lead to inaccurate determination of the apparent density using pycnometry. Thus, the determination of the apparent densities of all powder systems was repeated with samples that were subjected to loss on drying analysis, as the adsorbed moisture content of the samples would have been lost. The apparent densities for all powders before and after drying are listed below (Table 3.7.).

Powder	APD Before drying	APD After drying	t-test p
Orphenadrine Citrate	1.245 (0.024)*	1.225 (0.009)*	0.146
Orphenadrine Hydrochloride	1.166 (0.027)*	1.153 (0.016)*	0.371
Xanthan Gum	1.542 (0.006)*	1.552 (0.008)*	0.048
Spray Dried Lactose	1.536 (0.006)*	1.528 (0.004)*	0.033
Dibasic Calcium Phosphate Dihydrate (Emcompress ®)	2.377 (0.015)*	2.367 (0.017)*	0.360
Magnesium Stearate	1.091 (0.021)*	1.087 (0.014)*	0.728

Table 3.7. Apparent powder density of drug and excipient powders before and after drying. *Standard deviation (n = 5). p: significance; error probability to just reject the null hypothesis (significant if $p<0.05$).

All runs were performed with five replicates, and the significance of the difference in powder apparent density, before and after drying, was investigated using the independent sample t-test.

Xanthan Gum was the only material to exhibit a significant but small increase in its determined apparent density after drying ($p= 0.048$). As for the other materials, they all exhibited a reduction in their determined apparent density after drying. The difference was significant with spray dried lactose ($p= 0.033$). The difference between the apparent densities of the four other materials, before and after drying was not significant.

The behaviour of the powders, in terms of their density variation, could be clarified by the results of the moisture analysis studies. Xanthan Gum was the only powder with a considerable amount of moisture content. Water adsorbed on the surface of the particles may lead to errors in the determination of the apparent density. Picker and Mielck (1996), when working with pure hydrophilic polymer powders, used thermogravimertic analysis to determine the moisture content of the hydrophilic polymers maintained at different relative humidities. They suggested the use of a correction factor for the calculation of the apparent density of polymer powders when placed at equilibrium at various relative humidities, taking into account the influence of polymer bound water. However, this suggestion was made for pure polymer powders when placed at equilibrium at various relative humidities, but when the polymer is incorporated into multi-component formulations, and then compacted into

pharmaceutical tablets, its hydration properties may be affected which makes it difficult to determine its hydration characteristics.

As for all the other powders used in this study, they contained low amounts of moisture, and thus, the heating process may have affected the structure of the powder particles. This effect, of course, varies from material to material depending on its properties.

3.3.4. Thermal Characterisation of Spray Dried Lactose:

As discussed previously, spray dried lactose is usually manufactured by spray drying a suspension of α-lactose monohydrate crystals. This technique results in a material that has varying percentages of crystalline and amorphous content. The amorphous form of lactose was reported to have several advantages such as better compaction properties (Sebhatu and Alderborn 1999) and higher aqueous solubility. However, certain disadvantages are also associated with this form, mainly its hygroscopicity (Vromans et al 1987), and low stability (Elamin et al 1995). Hence, it is crucial to determine the polymorphic behaviour of any spray dried lactose batch.

The thermal behaviour of the spray dried lactose batch used in this study was investigated using Differential Scanning Calorimetry (DSC), which was considered a simple qualitative technique for identifying the type of hydrate present and content of the amorphous form of lactose. The results are presented below (Figure 3.23.)

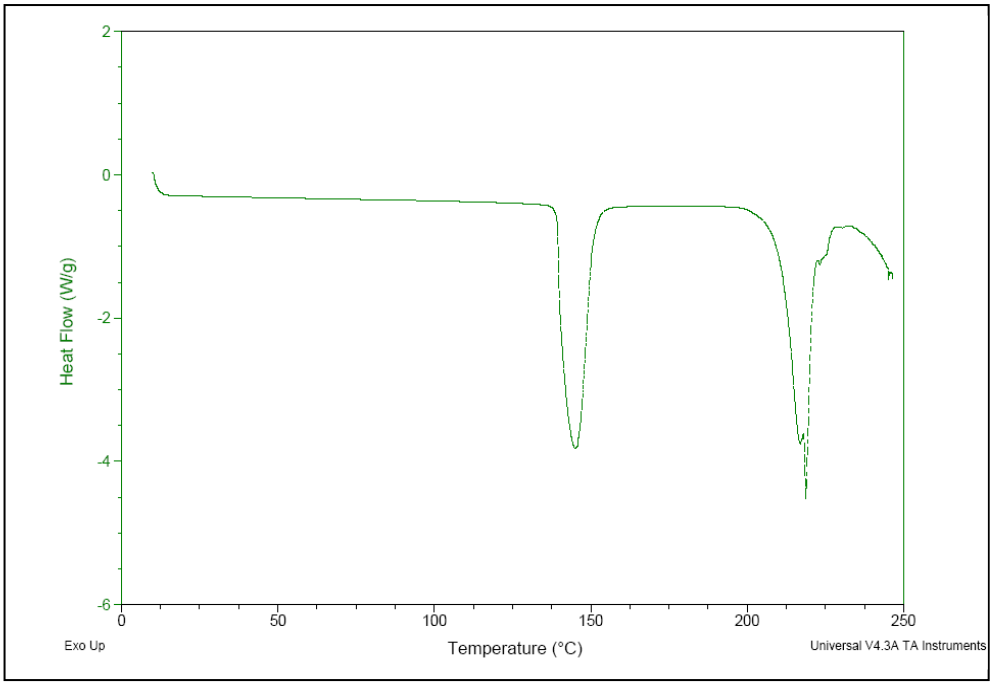

Figure 3.23. DSC thermogram of spray dried Lactose powder, heating rate 10°C/min, samples weight 5.1 mg.

The thermogram of the spray dried lactose batch used in the study exhibited a typical thermal behaviour associated with crystalline α-lactose monohydrate, showing a dehydration endothermic peak at about 146°C and a melting endothermic peak at about 220°C. This behaviour could be attributed to the conversion of the unstable amorphous form of lactose into the more stable crystalline form during the storage period.

As a quality control procedure the thermal investigation of the lactose batch was repeated at the start and the end of the study to monitor any change in behaviour. Similar results were obtained on both occasions, and thus it was possible to eliminate the potential influence of a change due to recrystallisation for this study.

3.4. General Discussion and Conclusions:

The results presented in this Chapter showed a varying nature in the physicochemical properties of the materials used in this study. In terms of the physicochemical properties of the two drugs used, Orphenadrine HCl is characterised by having a very small particle size value with a narrow particle size distribution. Whereas, Orphenadrine Citrate has a larger particle size value, and to an extent, a broader particle size distribution. This difference may have an influence on the physical properties of the different formulations used in this study. It could significantly influence their compaction properties, and the properties of the produced tablets. Moreover, this size difference, in association with the difference in the aqueous solubility between the two drugs, may have a marked influence on the hydration behaviour of the tablets, and on the process of drug release from them.

In terms of the polymer and the diluents used in this study, all of these materials exhibited rather broad particle size distributions. This was also accompanied by the presence of a large amount of fine particles.

CHAPTER FOUR

4. Production and physical characterisation of tablets

4.1 Introduction:

The influence of tablet properties, in terms of face curvature and porosity, on tablet physical behaviour, had been studied before using other types of pharmaceutical tablets. It was reported that these variables have a significant influence on the structural properties within the tablet, and on tablet tensile strength (Pitt et al 1989, 1990, Newton et al 2000a, 2000b, Djemai et al 2005). Such variables, and their subsequent influence on tablet properties, could have clear and major manifestations in hydrophilic matrix tablets, which undergo a hydration process initiated by water diffusion into the tablet and manifested by tablet swelling and expansion, all of which could be greatly affected by variation in tablet structural features.

It was hence the aim of this chapter to investigate fully the influence of such variables on the physical properties associated with the tablets used in this study. It was also attempted to clarify any observed variations

further using microscopic imaging techniques of the tablet structure. Another aim of this chapter was to elucidate how the influence of tablet face curvature, and that of tablet overall porosity, on the physical properties of the tablet vary when changing the nature of the formulation used in tablet production.

4.2. Choice of tablet parameters:

The choice of the particular tablet shapes used in this study was done to in order to have a representative model of the various degrees of tablet face curvature used normally in the pharmaceutical industry. Moreover, this selection was done to gain insight into the behaviour of tablets with a considerable variation in the nature of their structural properties.

4.2.1. Round tablets:

Four different degrees of tablet face curvature ratio were used for round tablets, as illustrated below (Figure 4.1.) and (Table 4.1). Moreover, the internal structural properties of all tablets were varied by using three different degrees of tablet overall porosity, i.e. 12.5%, 15% and 17.5%. Attempts to press tablets with the higher degrees of face curvature ratios of 1 and 1.43 at a lower porosity of 10% were not successful. Thus three degrees of tablet overall porosity were used.

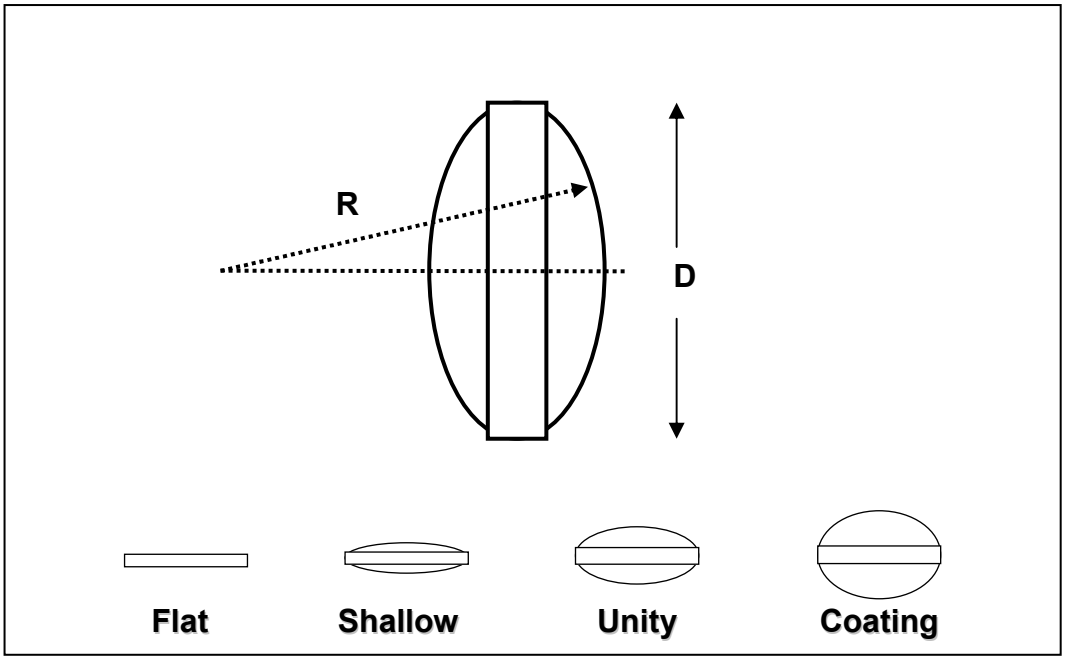

Figure 4.1: Schematic representation of the shape parameters of round tablets. R: radius of curvature, D: diameter.

Tablet Curvature	Radius of Curvature (mm)	Face Curvature Ratio (R/D)
Flat	0.00	0.00
Shallow	6.25	0.50
Unity	12.5	1.00
Coating	17.88	1.43

Table 4.1. Face curvature ratios of round tablets used. All tablets had a constant diameter of 12.5mm.

4.2.2. Elongated tablets:

Elongated tablets were used with three different degrees of curved segment height “a” of 0 mm “flat”, 1 mm and 2 mm (Figure 4.2.). In terms

of tablet porosity, it was not possible to produce elongated tablets with curved segment height of 2 mm at a porosity of 12.5%, thus, an upward shift in porosity values was undertaken resulting in three different degrees of tablet overall porosity of 15%, 17.5% and 20%.

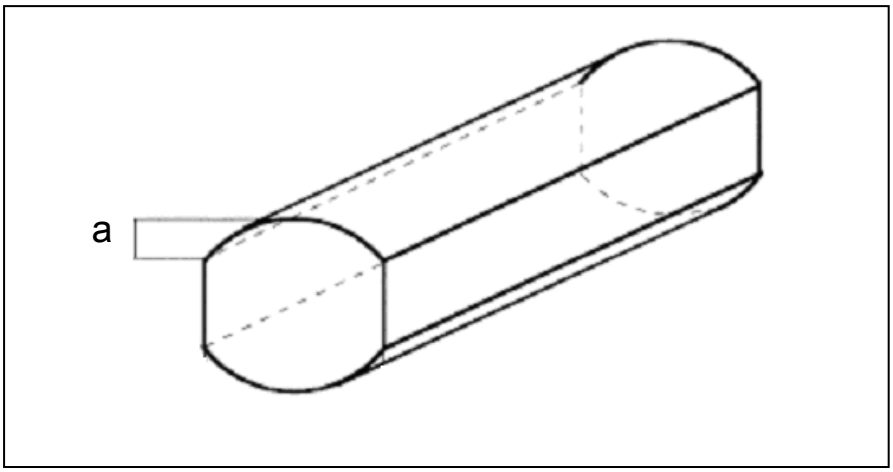

Figure 4.2. Schematic representation of shape parameters of elongated tablets, adapted from Newton et al (2000b).

A detailed description of the volume and shape parameters associated with all tablets used in this study are reported in the appendix.

4.3. Choice of formulations and tablet production:

A step wise experimental approach was adopted in the choice of the formulations used in this study. After initial selection of the hydrophilic polymer and drug substances, formulation development was carried out in parallel with tablet production. The main aim of this was to produce tablets with varying degrees of porosity, and sufficient physical strength to allow handling.

Multiple formulations were initially investigated, in which the contents of the diluents were varied. However, the three formulations listed in Table 4.2. were chosen because they allowed the production of tablets with the desired porosities and also with sufficient strength for handling.

Formulation Ingredients	Formulation percentage content		
	A	B	C
Xanthan Gum	47.5	35.0	35.0
Spray Dried Lactose	47.5	35.0	35.0
Dibasic Calcium Phosphate Dihydrate	4.0	4.0	4.0
Magnesium Stearate	1.0	1.0	1.0
Orphenadrine Citrate	0.0	25.0	0.0
Orphenadrine HCl	0.0	0.0	25.0

Table 4.2. Percentage contents of formulations used in tablet production.

Another factor taken into consideration during the process of formulation development was to keep the polymer content higher than that of the drug. This was sought to maintain a sufficient amount of the polymer for hydration in the presence of any interaction with the drug.

The apparent powder densities for the three formulation mixtures used in the study are presented below (Table 4.3.). Apart from Xanthan Gum, for all materials, the values for apparent powder density used were those obtained prior to subjecting the materials to loss on drying analysis, in order to avoid any influence cause by the possible changes in material

structure during the heating process. In the case of Xanthan Gum, the value used was that obtained for the dried Xanthan Gum sample. Once again this was done due to the high moisture content associated with the polymer powder.

Formulation	Apparent powder mixture density (g/cm^3)
A	1.573
B	1.498
C	1.479

Table 4.3. Apparent powder mixture densities of formulations used in tablet production.

A detailed description of the weight parameters associated with all the tablets used in the study is reported in the appendix.

4.4. Results and discussion:

4.4.1. Determination of the tensile strength of round tablets:

The tensile strength values of round tablets formulated with the three formulations used in this study are presented in Figures 4.3. to 4.5. The results are presented as a function of tablet face curvature. It is clearly evident from the figures that the influence of tablet structural properties; i.e. tablet face curvature and tablet porosity, on tablet tensile strength

values changes with the change in tablet formulation. For blank Xanthan Gum tablets (Figure 4.3.), increasing tablet face curvature ratio from 0 to 0.5, resulted in a drop in tablet tensile strength. Further increase in tablet face curvature ratio resulted in a progressive increase in tablet tensile strength, and this effect was observed in tablets produce at all three degrees of tablet overall porosity. A clear drop in tablet tensile strength was observed with the progressive increase in tablet overall porosity from 12.5% to 17.5%, and this influence was observed with all face curvature ratios.

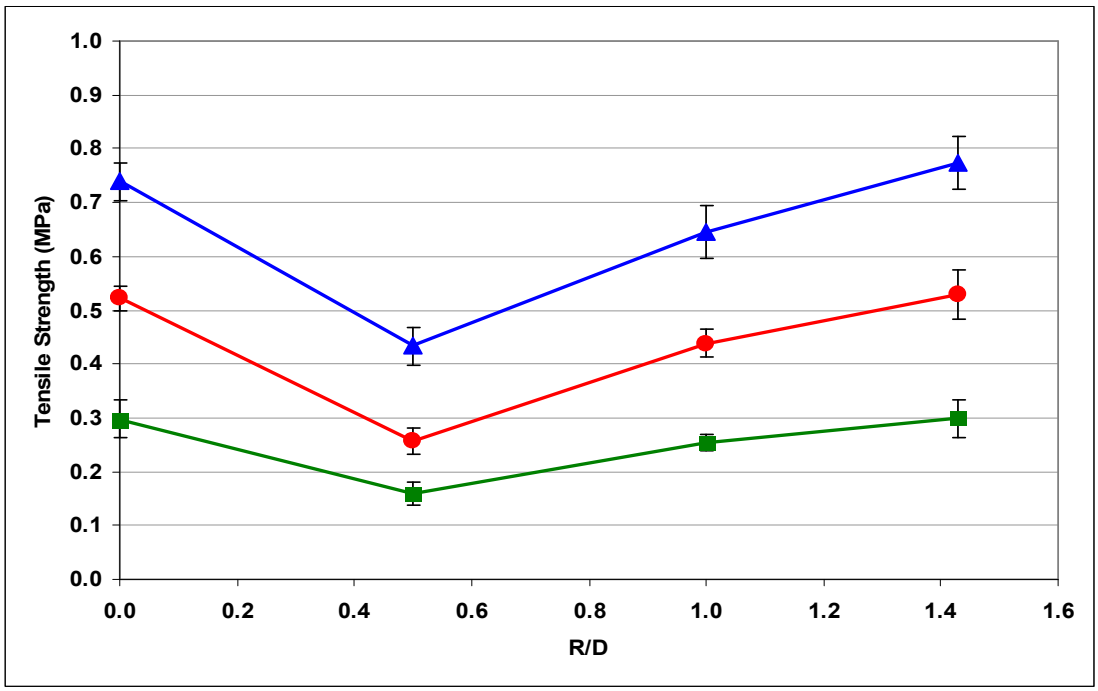

Figure 4.3. Tensile strength of round blank Xanthan Gum tablets. -▲- Porosity 12.5%, -●- Porosity 15%, -■-, Porosity 17.5%, (n = 6).

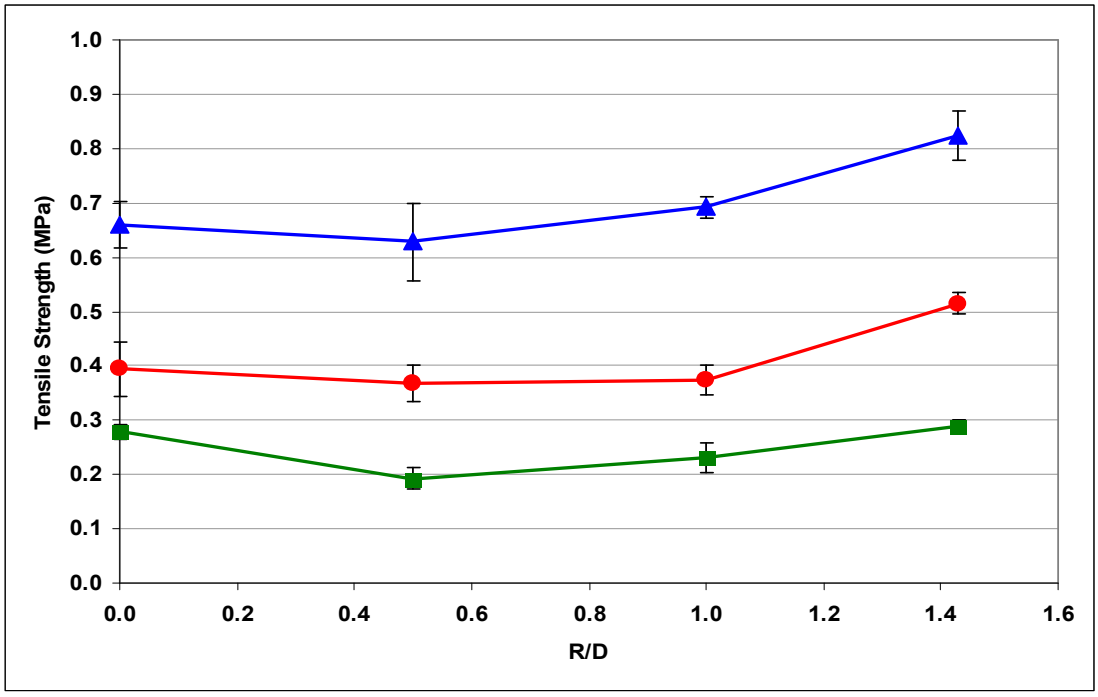

Figure 4.4. Tensile strength of round Xanthan Gum tablets with Orphenadrine Citrate. -▲- Porosity 12.5%, -●- Porosity 15%, -■-, Porosity 17.5%, (n = 6).

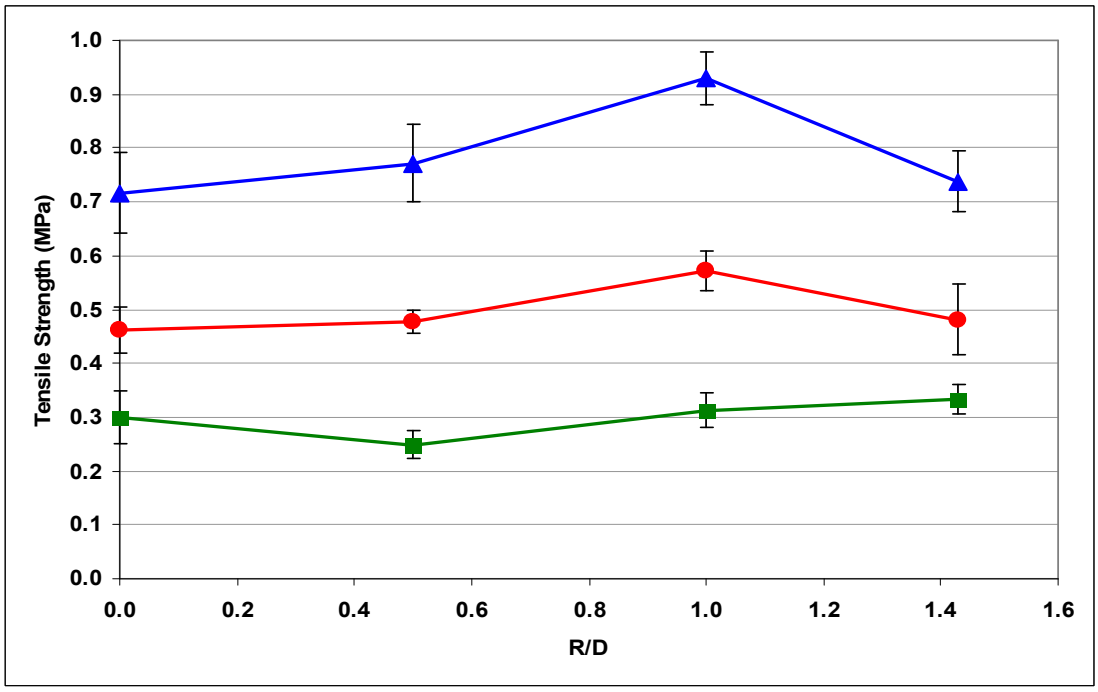

Figure 4.5. Tensile strength of round Xanthan Gum tablets with Orphenadrine HCl. -▲- Porosity 12.5%, -●- Porosity 15%, -■-, Porosity 17.5%, (n = 6).

Inclusion of either of the two drugs used in this study resulted in a clear change in tablet tensile strength values. For tablets containing the drug Orphenadrine Citrate (Figure 4.4.), a clear drop in tablet tensile strength was observed with the increase in tablet overall porosity from 12.5% to 17.5%. The influence of tablet face curvature ratio was different in comparison to blank tablets. Increasing tablet face curvature ratio from 0 to 0.5 resulted in a decrease in tablet tensile strength. Further increase in tablet face curvature ratio had a varying influence on tablet tensile strength for tablets produced at different overall porosity values. Tablets containing the drug Orphenadrine HCl (Figure 4.5.) exhibited a similar pattern in relation to the influence of tablet overall porosity. A clear drop in tablet tensile strength values was observed with the progressive increase in tablet overall porosity from 12.5% to 17.5%. This influence was also consistent with all face curvature ratios. The influence of tablet face curvature ratio was once again highly dependent on tablet overall porosity. For tablets produced at the two lower porosities of 12.5% and 15%, a progressive increase in tablet tensile strength was observed with the progressive increase in tablet face curvature ratio from 0 to 1. This was followed by a drop in tablet tensile strength upon further increase in tablet face curvature ratio from 1 to 1.43. For tablets produced at the higher overall porosity of 17.5%, a decrease in tablet tensile strength was observed upon increase in tablet face curvature ratio from 0 to 0.5. This was followed by a progressive increase in tablet tensile strength with further increase in tablet face curvature ratio from 0.5 to 1.43.

4.4.2. Statistical analysis of tensile strength values of round tablets:

The variation of tablet tensile strength values among the three formulations used in this study, and the clear influence of this variable on the effects induced by the changes in tablet face curvature and porosity, necessitated further elucidation of the differences between the tensile strength values obtained for the various tablets studied.

This statistical comparison of the tensile strength values of round tablets used in this study was accomplished by the use of analysis of variance (ANOVA) which is one of the powerful statistical analysis methods used in the comparison of the means of two or more groups of samples. The principle of this analysis depends on the comparison between the variability between the different groups with the variability within each of the separate groups through the use of the F-ratio which is calculated by dividing the variance between groups by that within the groups. The larger the F-ratio, the more indication of the presence of variability between groups (Pallant 2005). The computer calculates the precise error probability at which the Null hypothesis can just be rejected. If the value of the calculated error probability is equal to or less than a threshold of 0.05, then this can be accepted as significant difference.

For the analysis of the tensile strength values of round tablets used in this study, a multiple process of variance analysis was adopted. Initially, two-way ANOVA, which requires the presence of two independent categorising factors or variables under investigation, was carried out for

each formulation separately to investigate the significance of any effect induced by the change of tablet face curvature and porosity on tablet tensile strength. Further elucidation of the results was accomplished by a series of one-way ANOVAs, which were carried out for each value of overall porosity separately. This was done to investigate the influence of tablet face curvature on tablet strength and how this effect changes with changes in tablet overall porosity.

4.4.2.1. Round blank Xanthan Gum tablets:

The results of the two-way ANOVA for the tensile strength values of round blank Xanthan Gum tablets are shown in Table 4.4. The results indicate a significant influence of tablet overall porosity on tablet tensile strength with an F ratio of 790.185 corresponding to a p value of less than 0.001. A significant influence was also observed for tablet face curvature ratio with an F ratio of 199.287 corresponding to a p value of less than 0.001. The influence of tablet overall porosity seems to be more significant. This is indicated by the higher F ratio. However, and more importantly, the interaction product between tablet overall porosity and tablet face curvature ratio also has a significant influence on tablet tensile strength with an F ratio of 10.232 corresponding to a p value of less than 0.001. Such interaction is clearly evident in Figure. 4.3.; the magnitude of the difference between the tensile strength values for tablet with different face curvature ratios seems to decrease with the progressive increase in tablet overall porosity.

In order to give a clear picture for the interaction between tablet porosity and tablet face curvature ratio, one-way ANOVA was carried out for each of the three values of tablet overall porosity separately, to investigate the differences between tablets with different face curvature ratios. The results (Table 4.5.) indicate that tablet face curvature ratio had a significant influence on the tensile strength of tablets with all three overall porosity values.

Variable	df	F	p
Porosity	2	790.185	< 0.001
Curvature	3	199.287	< 0.001
Porosity*Curvature	6	10.232	< 0.001

Table 4.4. Results of the two-way ANOVA for the tensile strength of round blank Xanthan Gum tablets.

Porosity	df	F	p
12.5%	3	77.033	< 0.001
15.0%	3	100.098	< 0.001
17.5%	3	32.221	< 0.001

Table 4.5. Results for the one-way ANOVA for the tensile strength of round blank Xanthan Gum tablets, with different face curvature ratios.

Further insight into the significant effect as a result of the change in tablet face curvature ratio on tablet tensile strength (Table 4.5.) was accomplished by post hoc analysis using the Sheffé test, the use of which was justified due to the high significance associated with the studied variable; i.e. tablet face curvature ratio.

The results for the post hoc analysis for tablets produced at overall porosity values of 12.5%, 15% and 17.5% are listed in Tables 4.6. to 4.8.

		Subset		
Curvature	N	1	2	3
0.5	6	.43381		
1	6		.64580	
0	6			.73980
1.43	6			.77275
Sig.		1.000	1.000	.623

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.6. Results for the Sheffé post-hoc analysis test for round blank Xanthan Gum tablets, porosity 12.5%.

		Subset		
Curvature	N	1	2	3
0.5	6	.25724		
1	6		.43866	
1.43	6			.52172
0	6			.52998
Sig.		1.000	1.000	.975

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.7. Results for the Sheffé post-hoc analysis test for round blank Xanthan Gum tablets, porosity 15.0%.

Curvature	N	Subset 1	Subset 2
0.5	6	.15943	
1	6		.25353
1.43	6		.29754
0	6		.29878
Sig.		1.000	.083

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.8. Results for the Sheffé post-hoc analysis test for round blank Xanthan Gum tablets, porosity 17.5%.

The outcome of the Sheffé analysis groups the mean tensile strength values for the different levels of the studied variable into progressive subsets; the values grouped into the same subset are considered to have no significant difference between them. However, those grouped into different subsets are considered significantly different. The results for tablets with an overall porosity of 12.5% (Table 4.6.) show three different subsets. Tablets with a face curvature ratio of 0.5 have the lowest tensile strength value, followed by tablets with a face curvature ratio of 1. The highest tensile strength values were obtained with tablets with a face curvature ratio of 0 and 1.43, and these values are statistically similar. A similar pattern is obtained with tablets having an overall porosity of 15%. However, further increase in tablet overall porosity resulted in two subsets only. Tablets with a face curvature ratio of 0.5 had a mean tensile strength value that is significantly lower than tablets produced at the three other levels of face curvature ratio which were statistically similar.

4.4.2.2. Round Xanthan Gum tablets with Orphenadrine Citrate:

The results of the two-way ANOVA for the tensile strength of round Xanthan Gum tablets with Orphenadrine Citrate (Table 4.9.) indicated a highly significant influence of tablet overall porosity on tablet tensile strength with an F ratio of 964.245 corresponding to a p value of less than 0.001. A significant influence was also observed for tablet face curvature ratio with an F ratio of 53.418 corresponding to a p value of less than 0.001. Moreover, similar to the blank tablets, the interaction between the two variables; tablet overall porosity and face curvature ratio, had a significant influence on tablet tensile strength with an F ratio of 5.499 corresponding to a p value of less than 0.001.

The results of the one-way ANOVA for tablets with the three degrees of overall porosity are listed in Table 4.10. and they indicate a significant effect induced by the change in tablet face curvature on tablet tensile strength, for all degrees of tablet overall porosity.

Variable	df	F	p
Porosity	2	964.245	< 0.001
Curvature	3	53.418	< 0.001
Porosity*Curvature	6	5.499	< 0.001

Table 4.9. Results of the two-way ANOVA for the tensile strength of round Xanthan Gum tablets with Orphenadrine Citrate.

Porosity	df	F	p
12.5%	3	18.935	< 0.001
15.0%	3	23.327	< 0.001
17.5%	3	30.748	< 0.001

Table 4.10. Results for the one-way ANOVA for the tensile strength of round Xanthan Gum tablets with Orphenadrine Citrate, with different face curvature ratios.

The results of the post hoc Sheffé analysis for tablets with overall porosities of 12.5% and 15% (Tables 4.11. and 4.12.) show a similar pattern; two subsets were obtained, the first of which contained the mean strength values for tablets with face curvature ratios of 0, 0.5 and 1. Thus, these values are considered statistically similar. A significantly higher strength value was obtained with tablets having a face curvature ratio of 1.43, which is placed in a separate subset.

Upon further increase in tablet overall porosity a different outcome was obtained (Table 4.13.); the output of the Sheffé test had three subsets, the first contained the mean strength values for tablets with face curvature ratios of 0.5. The second contained those of tablets with a face curvature ratio of 1, and the third contained the mean strength values for tablets with face curvature ratios of 0 and 1.43. These values were statistically similar, and significantly higher than the values obtained for tablets with face curvature ratios of 0.5 and 1.

Curvature	N	Subset 1	Subset 2
0.5	6	.62818	
0	6	.65900	
1	6	.69150	
1.43	6		.82238
Sig.		.192	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.11. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine Citrate, porosity 12.5%.

Curvature	N	Subset 1	Subset 2
1	6	.36859	
0.5	6	.37442	
0	6	.39398	
1.43	6		.51487
Sig.		.667	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.12. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%.

Curvature	N	Subset 1	Subset 2	Subset 3
0.5	6	.19220		
1	6		.23096	
0	6			.27860
1.43	6			.28848
Sig.		1.000	1.000	.860

Means for groups in homogeneous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = .05.

Table 4.13. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine Citrate, porosity 17.5%.

4.4.2.3. Round Xanthan Gum tablets with Orphenadrine HCl:

The results for the two-way ANOVA for round Xanthan Gum tablets with Orphenadrine HCl are listed in Table 4.14. The results are somewhat similar to those obtained for tablets made using the two other formulations; tablet overall porosity had a highly significant influence on tablet tensile strength with an F ratio of 602.155 corresponding to a p value of less than 0.001. A significant influence was also obtained for the variable “tablet face curvature ratio”, but with a lower value for the F ratio of 20.321 corresponding to a p value of less than 0.001. The interaction between the two previous variables had also a significant influence on tablet tensile strength with an F ratio of 6.191 corresponding to a p value of less than 0.001.

Variable	df	F	p
Porosity	2	602.155	< 0.001
Curvature	3	20.321	< 0.001
Porosity*Curvature	6	6.191	< 0.001

Table 4.14. Results for the two-way ANOVA for the tensile strength of round Xanthan Gum tablets with Orphenadrine HCl.

One-way ANOVA was also carried out for tablets with different degrees of overall porosity. The results (Table 4.15.) indicate a significant effect of tablet face curvature ratio on tablet tensile strength at all three levels of

tablet overall porosity. The results of the Sheffé analysis for these tablets are shown in Tables 4.16. to 4.18.

Porosity	df	F	p
12.5%	3	13.658	< 0.001
15.0%	3	7.764	0.001
17.5%	3	6.641	0.003

Table 4.15. Results for the one-way ANOVA for the tensile strength of round Xanthan Gum tablets with Orphenadrine HCl, with different face curvature ratios.

		Subset	
Curvature	N	1	2
1.43	6	.71615	
0	6	.73812	
0.5	6	.77093	
1	6		.92932
Sig.		.544	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.16. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine HCl, porosity 12.5%.

		Subset	
Curvature	N	1	2
0	6	.46114	
0.5	6	.47651	
1.43	6	.48051	
1	6		.57255
Sig.		.902	1.000

Means for groups in homogeneous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = .05.

Table 4.17. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%.

Curvature	N	Subset 1	Subset 2
0.5	6	.24893	
0	6	.29907	.29907
1	6		.31337
1.43	6		.33410
Sig.		.130	.400

Means for groups in homogeneous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = .05.

Table 4.18. Results for the Sheffé post-hoc analysis test for round Xanthan Gum tablets with Orphenadrine HCl, porosity 17.5%.

A similar trend is noted in the Sheffé output of tablets with overall porosity of 12.5% and 15%. Two Subsets are present, the first of which contained the statistically similar mean strength values for tablets with face curvature ratios of 0, 0.5 and 1.43. The second subset contained the mean tensile strength value for tablets with a face curvature ratio of 1. This value was significantly higher than the values obtained with all other tablets. Two subsets were also present in the Sheffé output for tablets with an overall porosity of 17.5%, the first of which contained the mean strength values for tablets with a face curvature ratio of 0.5 and 0. The second subset contained the mean strength values for tablets with face curvature ratios of 0, 1, and 1.43. Such result indicate that the only statistically significance difference occurred between the tensile strength values of tablets with face curvature ratios of 0.5 and those with ratios of 1, and 1.43 which were significantly higher. No statistically significant differences were noted between the tensile strength values of flat tablets and those of tablets with any of the other face curvature ratios.

The results of the statistical analysis for the tensile strength values of round tablets indicated some similar trends where both tablet overall porosity and to a lesser extent tablet face curvature ratio had a significant influence on tablet tensile strength. Moreover, the interaction between these two variables had a significant influence on tablet tensile strength. Further investigation of this interaction clearly demonstrated that round tablets produced at similar overall porosity values but with different face curvature ratios, vary in their tensile strength values. Such findings are in agreement with previous work carried out using other pharmaceutical materials (Newton et al 2000a). This behaviour could be attributed to the greater importance associated with the actual pore shape and size on the tensile strength of tablets, when compared to the importance associated with the overall porosity of the tablets (Rice 1993). Producing tablets using punches with varying degrees of face curvature could lead to different patterns of powder movement and densification within the tablet (Eiliazadeh et al 2003, 2004). This in turn could lead to different patterns of density and hence porosity distribution within tablets having different degrees of face curvature.

Tablet failure upon being subjected to diametral compression is highly associated with the formation of cracks in the tablet structure. Tablet pores, although not considered as being part of flaws in the structure of the tablet, form the starting point for crack formation and propagation (Rice 1984). Thus, the actual shape and size of the individual pores could have a clear influence on tablet tensile strength.

In terms of the influence of the type of formulation on the tensile strength of round tablets, it becomes evident from monitoring the tensile strength values associated with the various round tablets (Figures 4.3. to 4.5.) that the change in tablet tensile strength upon changing the face curvature ratio of the tablet and the tablet overall porosity, is highly influenced by the change in the formulation used in the production of the tablets. Such variation arises mainly from the change in the physical properties of the powders incorporated into the different formulations. Such changes, especially the change in powder particle size and compaction properties, would lead to significant changes in the internal structure of the tablet.

4.4.3. Determination of the tensile strength of elongated tablets:

The tensile strength values for blank and drug containing elongated tablets are presented in Figures (4.6. to 4.8.). Values are presented as a function of tablet curved segment height. Once again, it is clearly evident, that a change in tablet formulation caused a clear variation in the tensile strength values obtained for the different tablets. Upon inspection of the results obtained for blank Xanthan Gum tablets (Figure 4.6.), it was evident that increasing the height of the curved segment in the tablet from 0 to 2mm resulted in a progressive increase in tablet tensile strength. A clear drop in tensile strength values was observed with the increase in tablet overall porosity from 15% to 20% progressively. Furthermore, the extent of increase in tablet tensile strength as a function of the increase in curved segment height varied between the different degrees of tablet

overall porosity, and seemed to flatten with the increase in tablet overall porosity.

Tablets containing the drug Orphenadrine Citrate (Figure 4.7.) exhibited a somewhat different behaviour; an increase in tablet tensile strength was observed upon increase of curved segment height from 0 to 1 mm. Further increase in curved segment height from 1mm to 2 mm resulted in a minimal increase in tablet tensile strength in comparison to blank tablets. The effect of tablet overall porosity was also evident in these tablets; a drop in tablet tensile strength was found as a result of the progressive increase in tablet overall porosity from 15% to 20%.

Tablets containing the drug Orphenadrine HCl (Figure 4.8.) exhibited a clear drop in tablet tensile strength with the progressive increase in tablet overall porosity. In terms of the effect associated with the height of the curved segment in the tablet, increasing this height from 0 to 2 mm resulted in a progressive increase in tablet tensile strength. Moreover, this effect also varied with the variation in tablet overall porosity.

Tablets containing the drug Orphenadrine HCl had tensile strength values that were consistently higher than those obtained with blank tablets and tablets containing the drug Orphenadrine Citrate. Such effect could be caused by the different nature of the internal structure of tablets produced using the three different formulations.

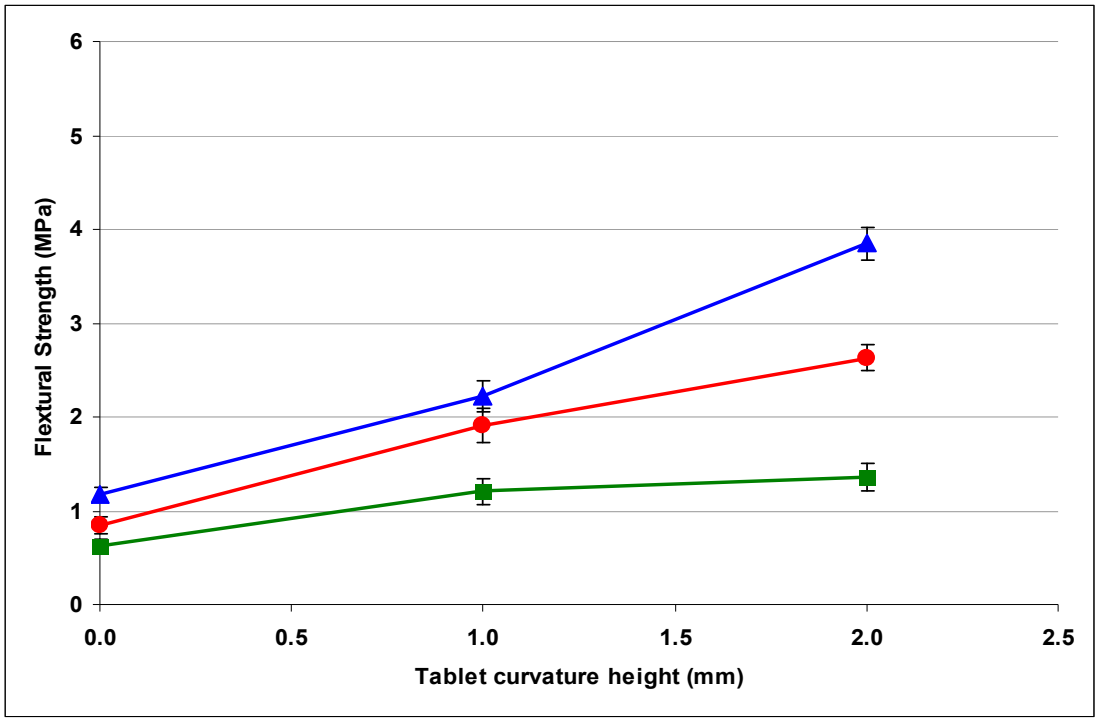

Figure 4.6. Tensile strength of elongated blank Xanthan Gum tablets. -▲- Porosity 15%, -●- Porosity 17.5%, -■-, Porosity 20%, (n = 6).

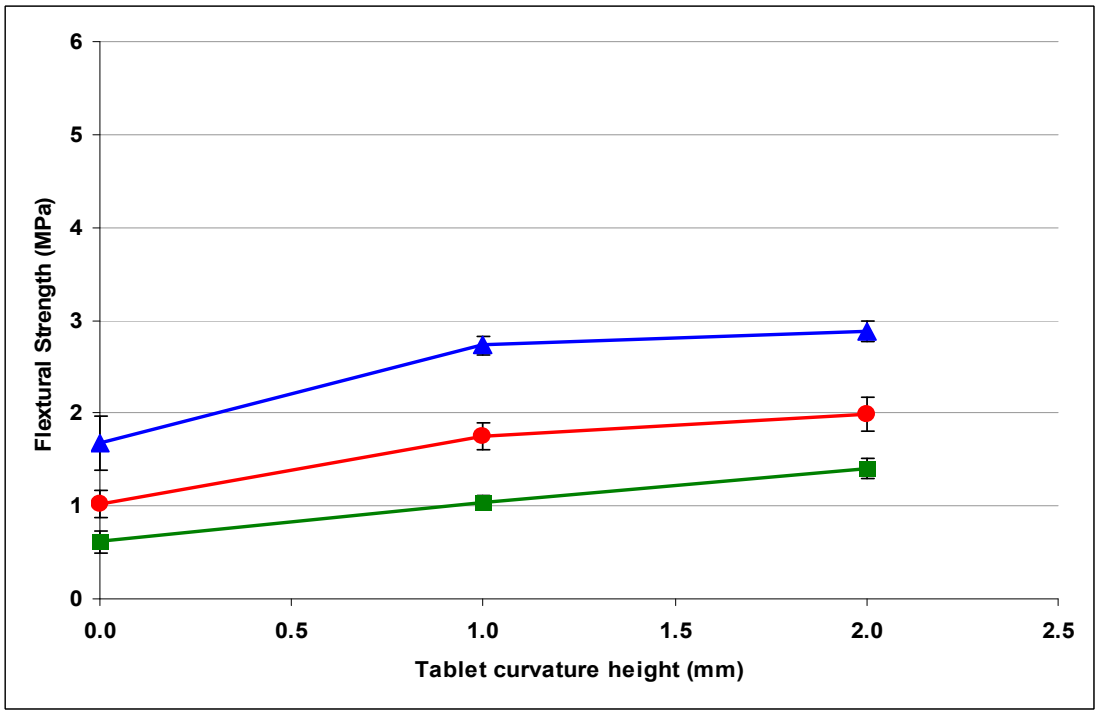

Figure 4.7. Tensile strength of elongated Xanthan Gum tablets with Orphenadrine Citrate. -▲- Porosity 15%, -●- Porosity 17.5%, -■-, Porosity 20%, (n = 6).

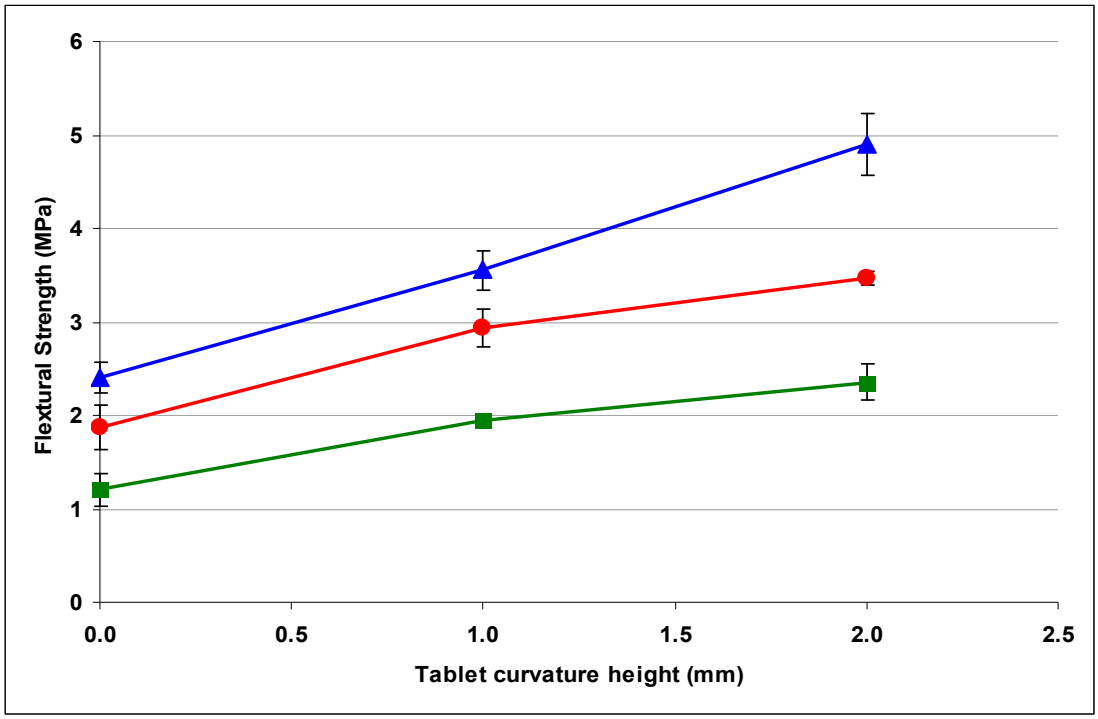

Figure 4.8. Tensile strength of elongated Xanthan Gum tablets with Orphenadrine HCl. -▲- Porosity 15%, -●- Porosity 17.5%, -■-, Porosity 20%, (n = 6).

The results obtained in this study are in agreement with previously reported work, which indicated an increase in the tensile strength of elongated tablets with progressive increase in the height of the curved segment of the tablet, and a progressive decrease in tablet tensile strength values with increased tablet porosity (Newton et al 2000b).

4.4.4. Statistical analysis of tensile strength values of elongated tablets:

In a similar manner to round tablets, the tensile strength values for elongated tablets were subjected to statistical analysis comprising a combination of two-way and one-way ANOVA, in order to clearly

elucidate the influence of tablet properties, in terms of curvature height and overall porosity, on the tensile strength of tablets produced using the three formulations used in this study.

4.4.4.1. Elongated blank Xanthan Gum tablets:

The results of the two-way ANOVA for elongated blank Xanthan Gum tablets are shown in Table 4.17. They indicate a significant influence as a result of the change in tablet porosity on tablet tensile strength with an F ratio of 434.771 corresponding to a p value of less than 0.001. The influence of tablet curvature height on tablet tensile strength was also significant with an F ratio of 715.335 corresponding to a p value of less than 0.001. The magnitude of the influence associated with the change in tablet face curvature seems to be higher than that associated with tablet overall porosity, which is apparent from the value of the F ratio associated with each of them. More importantly, the interaction between the two previous variables also had a significant influence on the tensile strength of tablets.

Variable	df	F	p
Porosity	2	434.771	< 0.001
Curvature	2	715.335	< 0.001
Porosity*Curvature	4	83.609	< 0.001

Table 4.19. Results for the two-way ANOVA for the tensile strength of elongated blank Xanthan Gum tablets.

Further investigation of the significant interaction between tablet overall porosity and tablet curvature height was accomplished by a series of one-way ANOVA to elucidate the influence of changing tablet curvature height on tablet tensile strength. Separate investigations were carried out for tablets with the three degrees of overall porosity, the results of which are reported in Table 4.18. The values of the F ratio and the corresponding p value for each porosity level revealed a significant influence of tablet curvature height on tablet tensile strength values.

Porosity	df	F	p
15.0%	2	523.821	< 0.001
17.5%	2	238.906	< 0.001
20.0%	2	57.437	< 0.001

Table 4.20. Results for the one-way ANOVA for the tensile strength of elongated blank Xanthan Gum tablets, with different curvature heights.

In a manner, similar to that used with round tablets, post hoc Sheffé analysis was carried out to point out the significant differences between the degrees of tablet curvature height at all porosity levels. For tablets with overall porosities of 15% and 17.5%, a similar pattern was observed in the output of the Sheffé analysis. Three different subsets were obtained, containing the mean values of tablet tensile strength associated with the three different degrees of tablet curvature height progressively.

This indicates a significant increase in tablet tensile strength with the progressive increase in curvature height from 0 to 2 mm.

For tablets with an overall porosity of 20%, the output of the Sheffé analysis indicated two different subsets, the first of which contained the mean value for the tensile strength of flat tablets. The second subset contained the mean values for the tensile strength of tablets with the two higher degrees of curvature height of 1 and 2 mm. these statistically similar strength values are significantly higher that the strength value of flat tablets.

		Subset		
Curvature	N	1	2	3
0	6	1.16900		
1	6		2.21983	
2	6			3.84517
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.21. Results for the Sheffé post-hoc analysis test for elongated blank Xanthan Gum tablets, porosity 15.0%.

		Subset		
Curvature	N	1	2	3
0	6	.84117		
1	6		1.90950	
2	6			2.62900
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.22. Results for the Sheffé post-hoc analysis test for elongated blank Xanthan Gum tablets, porosity 17.5%.

Curvature	N	Subset 1	Subset 2
0	6	.62783	
1	6		1.20250
2	6		1.35800
Sig.		1.000	.130

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.23. Results for the Sheffé post-hoc analysis test for elongated blank Xanthan Gum tablets, porosity 20.0%.

4.4.4.2. Elongated Xanthan Gum tablets with Orphenadrine Citrate:

The results of the two-way ANOVA for elongated Xanthan Gum tablets with Orphenadrine Citrate are listed in Table 4.22. They indicate a significant influence of tablet overall porosity on tablet tensile strength with an F ratio of 390.319 corresponding to a p value of less than 0.001. The influence of tablet curvature height was also significant, with an F ratio of 205.358 corresponding to a p value of less than 0.001. In contrast to the blank elongated tablets, the magnitude of the influence associated with tablet overall porosity was higher than that associated with tablet curvature height and this is apparent from the higher F ratio.

Variable	df	F	p
Porosity	2	390.319	< 0.001
Curvature	2	205.358	< 0.001
Porosity*Curvature	4	6.389	< 0.001

Table 4.24. Results for the two-way ANOVA for the tensile strength of elongated Xanthan Gum tablets with Orphenadrine Citrate.

Once again, one-way ANOVA for all three levels of tablet overall porosity revealed a significant influence as a result of the change in tablet curvature height on the tensile strength values, as noted from the values of the F ratio and the corresponding p values in Table 4.23.

Porosity	df	F	p
15.0%	2	74.353	< 0.001
17.5%	2	62.489	< 0.001
20.0%	2	91.798	< 0.001

Table 4.25. Results for the one factorial ANOVA for the tensile strength of elongated Xanthan Gum tablets with Orphenadrine Citrate, with different curvature heights.

Post hoc analysis for the tensile strength values of these tablets indicated that at the lower porosity of 15% (Table 4.24.) the output of the Sheffé analysis contained two subsets, the first containing the mean strength value for flat tablets. However, the second subset contained the significantly higher mean strength values for tablets with curvature height of 1 and 2 mm.

The two higher overall porosities of 17.5% and 20% resulted in three significantly different subsets (Tables 4.25. and 4.26.), containing the mean strength values for tablets with the three degrees of curvature height progressively.

Curvature	N	Subset 1	Subset 2
0	6	1.67915	
1	6		2.73293
2	6		2.88537
Sig.		1.000	.391

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.26. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%.

Curvature	N	Subset 1	Subset 2	Subset 3
0	6	1.01843		
1	6		1.74697	
2	6			1.99505
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.27. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 17.5%.

Curvature	N	Subset 1	Subset 2	Subset 3
0	6	.61168		
1	6		1.04858	
2	6			1.40257
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.28. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 20.0%.

4.4.4.3. Elongated Xanthan Gum tablets with Orphenadrine HCl:

The results for the two-way ANOVA for elongated Xanthan Gum tablets with Orphenadrine HCl are listed in Table 4.27. A significant influence induced by the change in both tablet overall porosity and tablet curvature height was noted. The magnitude of such influence seems to be similar for both variables with an F ratio of 369.703 corresponding to a p value of less than 0.001 for tablet overall porosity, and an F ratio of 356.139 corresponding to a p value of less than 0.001 for tablet curvature height. Furthermore, in a manner consistent with all previous observations, the interaction between the two previous variables had a significant influence on tablet tensile strength with an F ratio of 19.788 corresponding to a p value of less than 0.001.

One-way ANOVA for tablets produced at the three levels of overall porosity revealed a significant influence as a result of the change in tablet curvature height on tablet tensile strength, as noted by the F ratios and the corresponding p values in Table 4.28.

Post hoc Sheffé analysis revealed a similar trend in tablets produced at all three degrees of overall porosity (Tables 4.29. to 4.31.). Each output contained three significantly different progressive subsets, containing the mean strength values for tablets with the three degrees of curvature height progressively.

Variable	df	F	p
Porosity	2	369.703	< 0.001
Curvature	2	356.139	< 0.001
Porosity*Curvature	4	19.788	< 0.001

Table 4.29. Results for the two-way ANOVA for the tensile strength of elongated Xanthan Gum tablets with Orphenadrine HCl.

Porosity	df	F	p
15.0%	2	155.767	< 0.001
17.5%	2	118.365	< 0.001
20.0%	2	89.285	< 0.001

Table 4.30. Results for the one-way ANOVA for the tensile strength of elongated Xanthan Gum tablets with Orphenadrine HCl, with different curvature heights

		Subset		
Curvature	N	1	2	3
0	6	2.40703		
1	6		3.55237	
2	6			4.90348
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.31. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%.

Curvature	N	Subset 1	Subset 2	Subset 3
0	6	1.86850		
1	6		2.93310	
2	6			3.47282
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.32. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 17.5%.

Curvature	N	Subset 1	Subset 2	Subset 3
0	6	1.20225		
1	6		1.93808	
2	6			2.35647
Sig.		1.000	1.000	1.000

Means for groups in homogenous subsets are displayed.
Sheffe test uses Harmonic Mean Sample Size = 6.000.
Alpha = 0.05.

Table 4.33. Results for the Sheffé post-hoc analysis test for elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 20.0%.

All the one-way and two-way ANOVA processes carried out during the statistical analysis of tensile strength data for both round and elongated tablets were preceded by a check for the homogeneity of variance between the studied samples in each test. The homogeneity of variance is a prerequisite for parametric comparisons of mean values. The test for it was accomplished using the Levene test, and the results indicated a homogeneity in variances of the samples used in most of the ANOVA tests. Some exceptions were noted, in which the results of the Levene

test indicated a significant difference between the variances of the studied samples. However, the use of ANOVA was justified in all cases for two reasons; initially, the F ratio is sufficiently robust to differences in sample variance when the sizes of the studied samples are equal (Stevens 1996), which is the case in this work. A uniform sample size of six tablets was adopted for all tests. Secondly, and more importantly, the influence level of the studied variables, in the cases were differences in sample variance were reported, was highly significant, with p values of less than 0.001. Thus clear differences were noted between the different samples. A list of the outputs of the ANOVA tests used in this work is included in the appendix.

In a manner similar to that observed with round tablets, the results of the tensile strength experiments conducted on elongated tablets (Figures 4.6. to 4.8.) clearly indicate a profound influence of the type of formulation used in tablet production on the effects exerted by the two dosage form related variables, i.e. tablet face curvature and tablet overall porosity.

4.4.5. Microscopic examination of tablet structure:

Scanning electron microscopy was used to give further insight into the structural features associated with the various types of tablets used in this study. The results obtained from the tensile strength determination studies indicated a large variation in the behaviour of the tablets produced using the three different formulations used in this study. This

variation, as was previously mentioned, could be related to the variation in the internal structural features of the tablets. Moreover, the overall appearance of the produced tablets was significantly different especially among the three formulations used. It was thus important to further investigate such variations, as they could influence tablet properties and behaviour.

4.4.5.1. Tablet Surface:

The nature of the surface properties associated with hydrophilic matrix tablets could have a significant influence on the initial phases of tablet hydration and drug release. Hence it was crucial to identify any variations in such properties between the various tablets used in this study.

Scanning electron microscopic images of the surface of blank and drug containing round flat tablets are presented in Figures 4.9. to 4.14. Closer inspection of the images reveals some variations in the surface structural properties associated with each formulation. Blank Xanthan Gum tablets (Figures 4.9. and 4.10.) could be characterised by having a rather rough surface due to the presence of large un-fragmented Xanthan Gum particles. Tablets containing the drug Orphenadrine Citrate had a less rough surface when compared to blank tablets (Figure 4.11.). Closer inspection of these tablets revealed a more compacted surface (Figure 4.12.). As for tablets containing the drug Orphenadrine HCl, the surface of these tablets was much smoother in comparison to tablets produced using the two other formulations (Figure 4.13.). Closer inspection of the

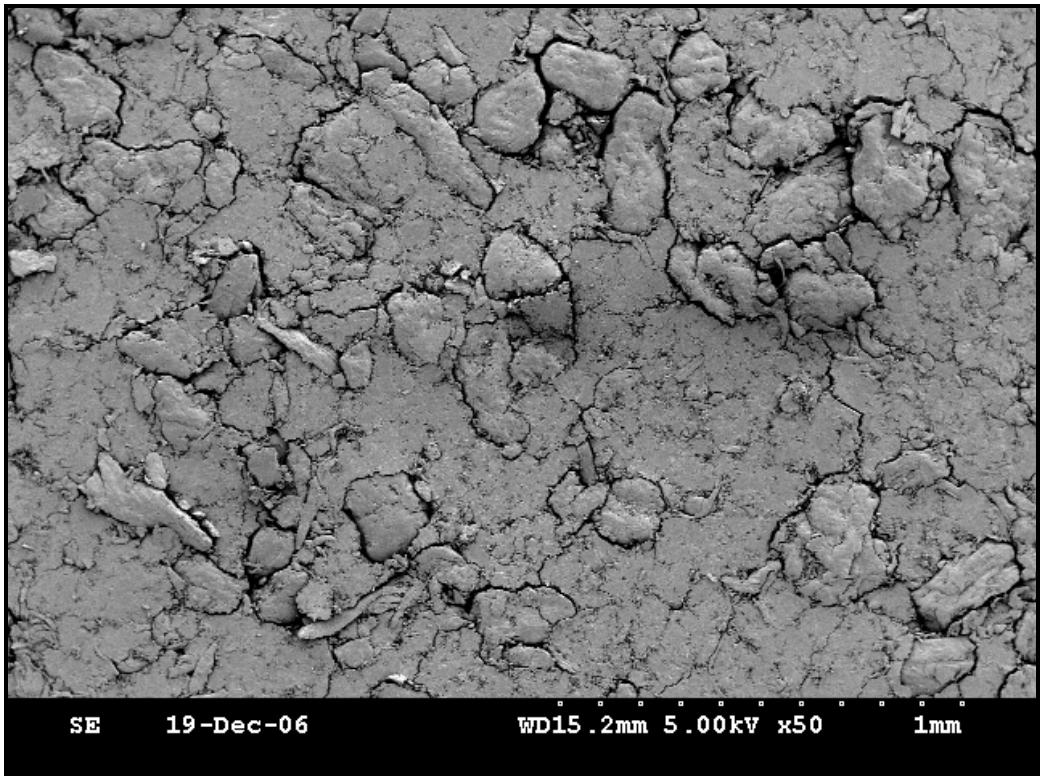

Figure 4.9. SEM images of the surface of flat round blank Xanthan Gum tablets with porosity of 15% (magn. 50X).

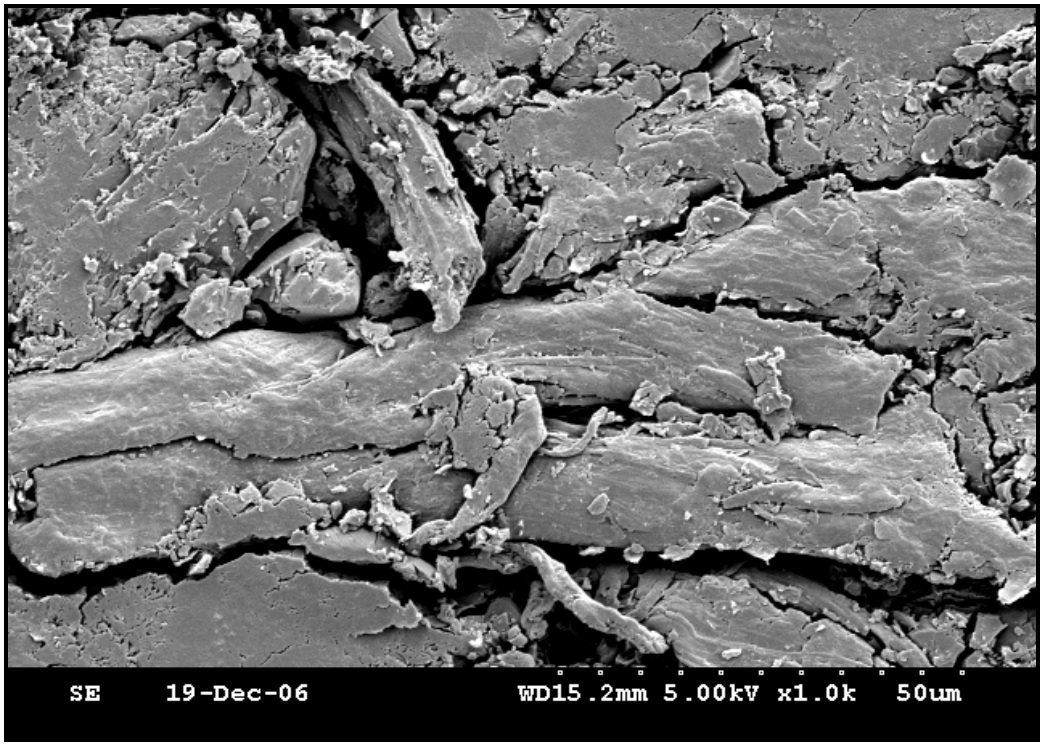

Figure 4.10. SEM images of the surface of flat round blank Xanthan Gum tablets with porosity of 15% (magn. 1000X).

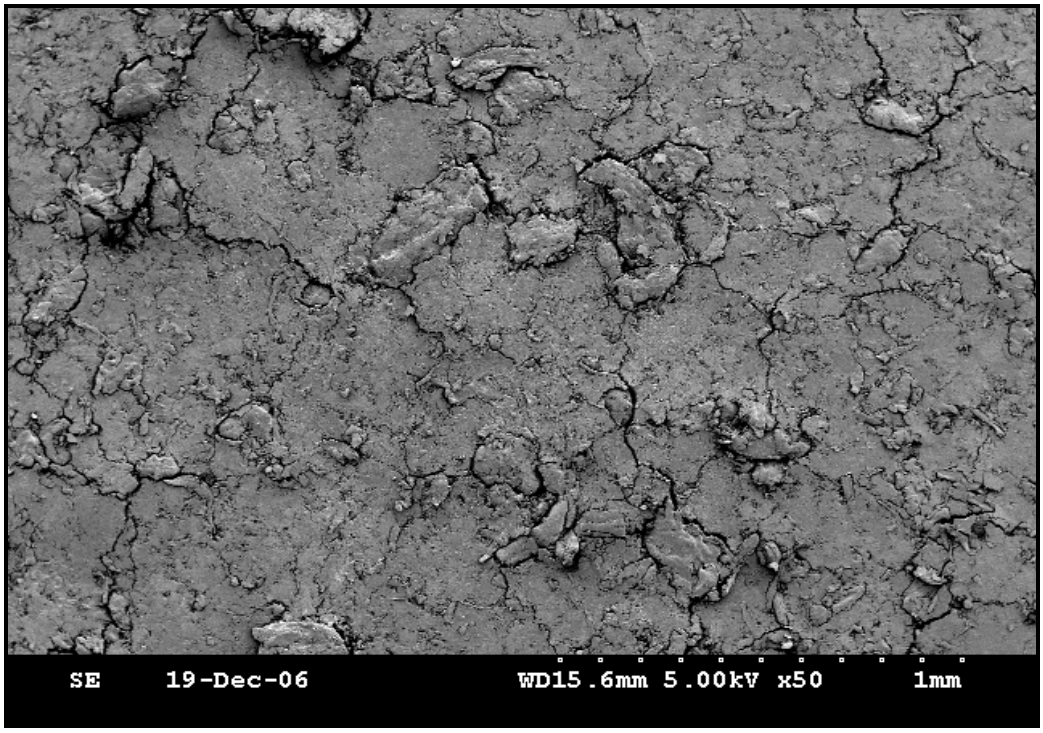

Figure 4.11. SEM images of the surface of flat round Orphenadrine Citrate tablets with porosity of 15% (magn. 50X).

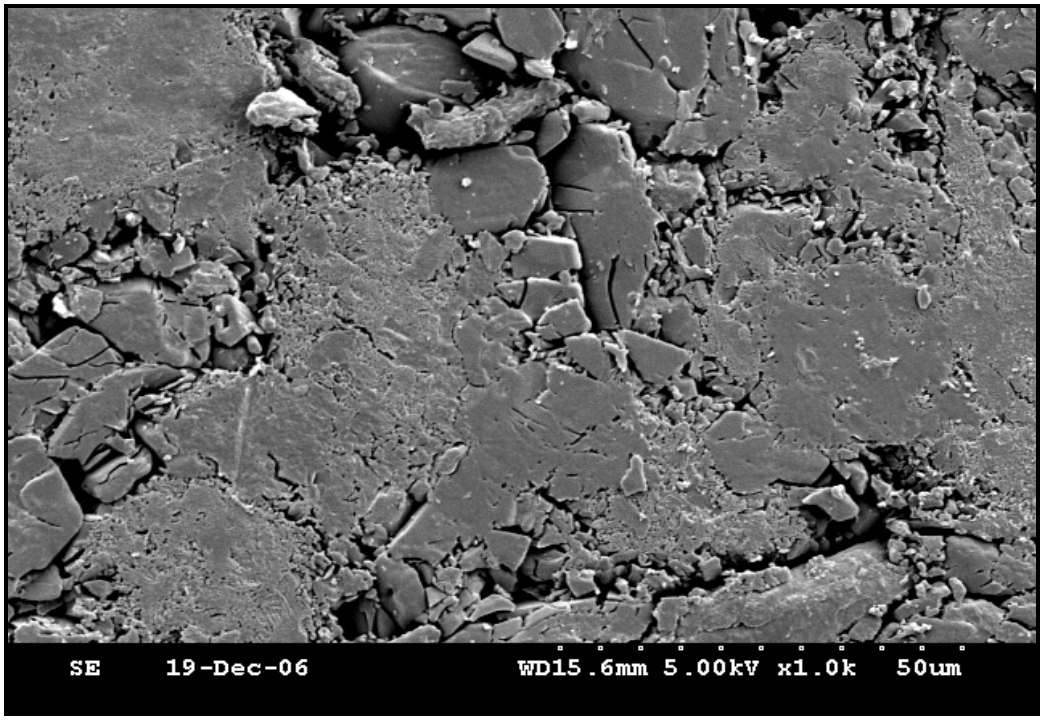

Figure 4.12. SEM images of the surface of flat round Orphenadrine Citrate tablets with porosity of 15% (magn. 1000X).

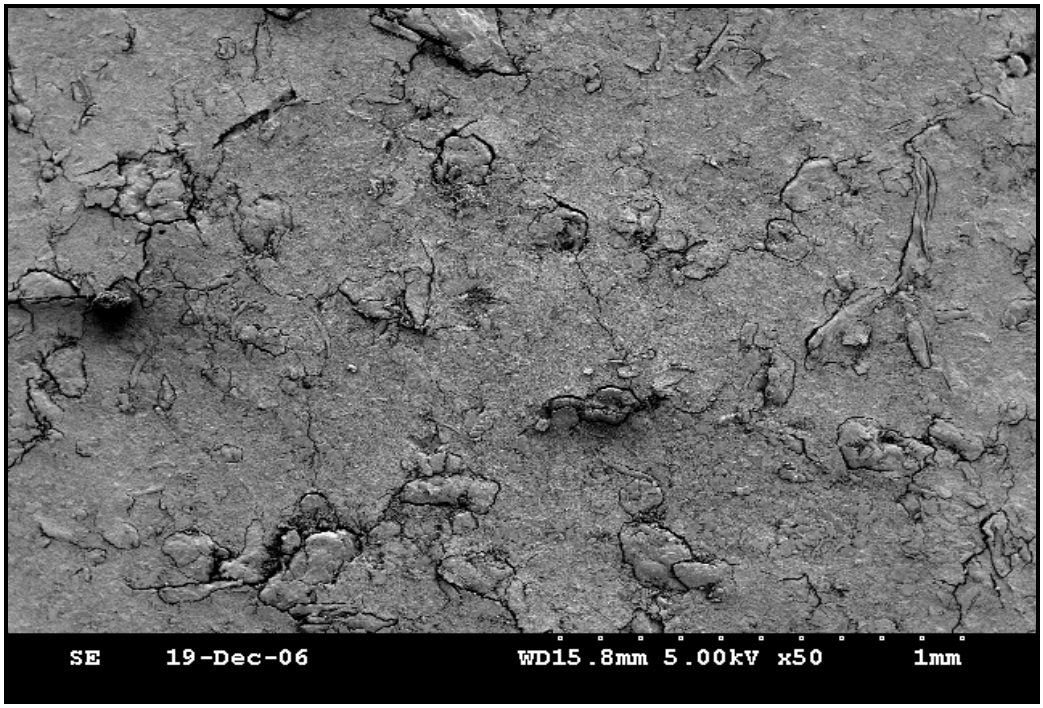

Figure 4.13. SEM images of the surface of flat round Orphenadrine HCl tablets with porosity of 15% (magn. 50X).

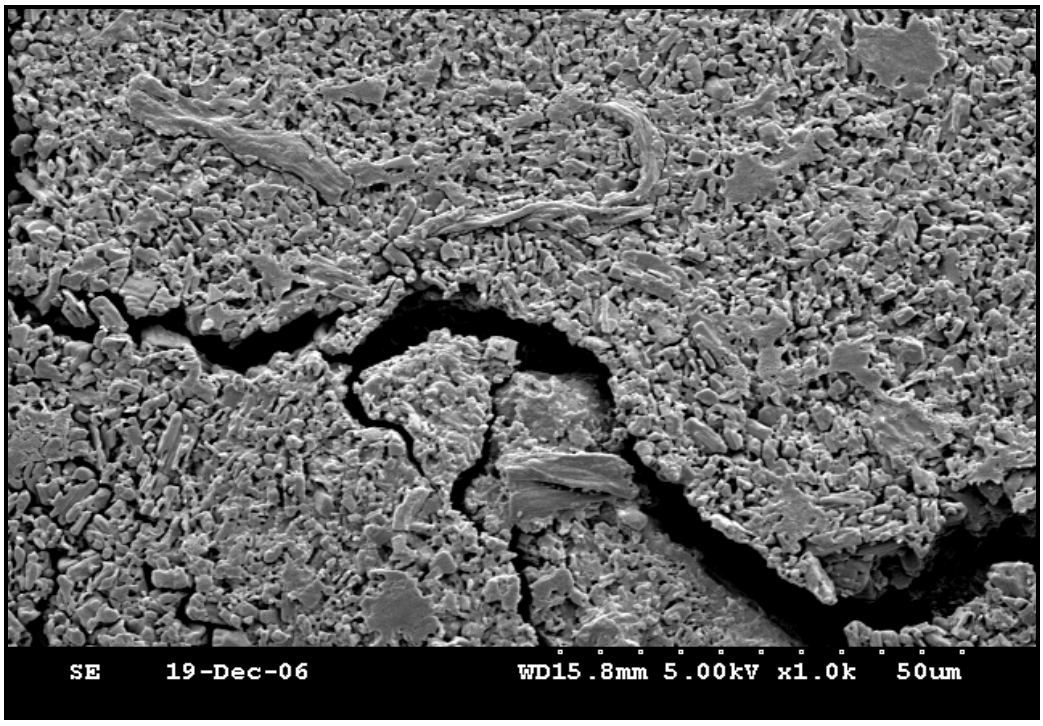

Figure 4.14. SEM images of the surface of flat round Orphenadrine HCl tablets with porosity of 15% (magn. 1000X).

surface of these tablets (Figure 4.14.), revealed the presence of a large number of fine particles with a high degree of compaction. Such an effect could be related to the previously reported fine particle size associated with this drug.

Fine cracks were noticed in tablets produced using all three formulations. However, the extent of the presence of such cracks was larger in blank tablets and tablets containing the drug Orphenadrine Citrate, with fewer cracks noticed in tablets containing the drug Orphenadrine HCl.

4.4.5.2. Tablet fracture surface:

The structural patterns associated with the fracture surface of the tablet could give an insight into the different fracture behaviours associated with the different tablets. Scanning electron microscopic images of the fracture surfaces of round convex tablets with a face curvature ratio of 1.43 are presented in Figures 4.15. to 4.20.

Initial comparison of tablets produced using the three different formulations at a low magnification power did not reveal significant differences between the tablets (Figures 4.15., 4.17. and 4.19.). Closer inspection of the fracture surface of blank Xanthan Gum tablets (Figure 4.16.) revealed the presence of a compacted structure composed mainly of large particles.

A rather similar pattern was observed upon the inspection of the fracture surface in tablets containing the drug Orphenadrine Citrate (Figure 4.18.). In these tablets, a somewhat higher degree of compaction could be observed, with the presence of some fine particles. However, for tablets containing the drug Orphenadrine HCl, a significantly different fracture surface was observed (Figure 4.20.). The surface was highly compacted with the presence of a large number of fine particles. This pattern, once again, could be attributed to the fine particle size of the drug.

The varying nature of the fracture surface properties associated with the three different formulations gives a clear insight into the change in the internal structure of the tablets. Such change, in turn, may have lead to the different tensile strength values obtained for tablets produced using the different formulations.

Upon comparing the surface and internal structural properties associated with flat and highly convex round tablets using scanning electron microscopy, minimal differences were observed. Thus, this technique was not useful in investigating this aspect with the formulations used in this study.

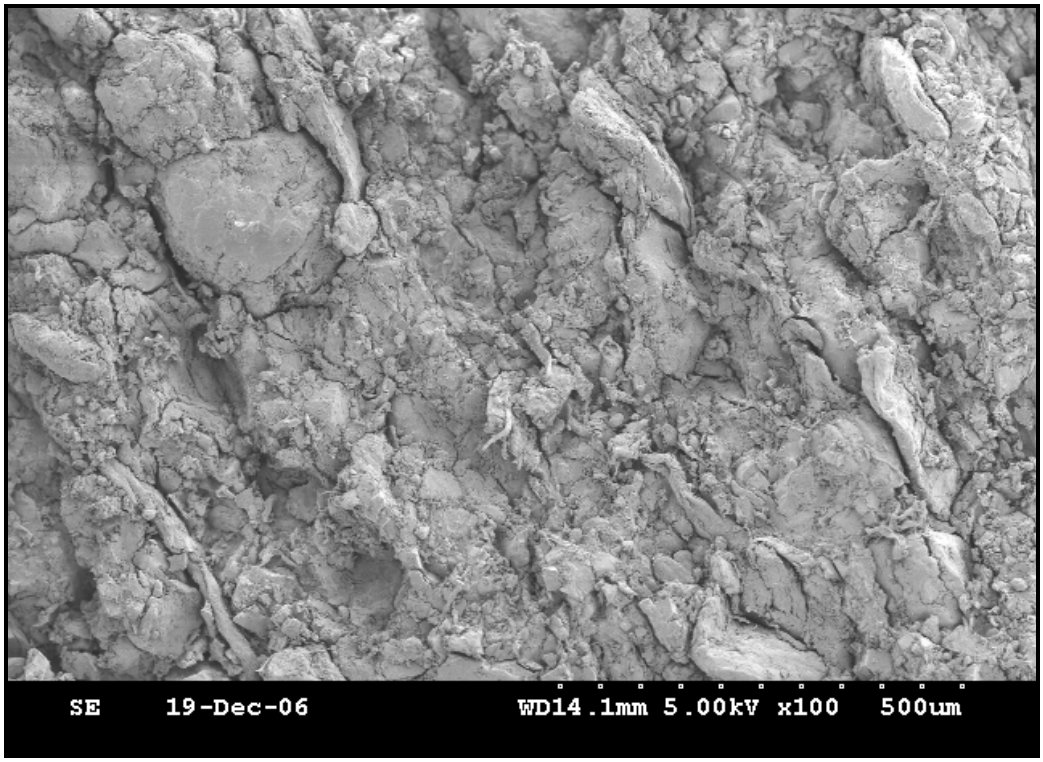

Figure 4.15. SEM images of the fracture surface of round blank Xanthan Gum tablets with porosity of 15% (magn. 100X).

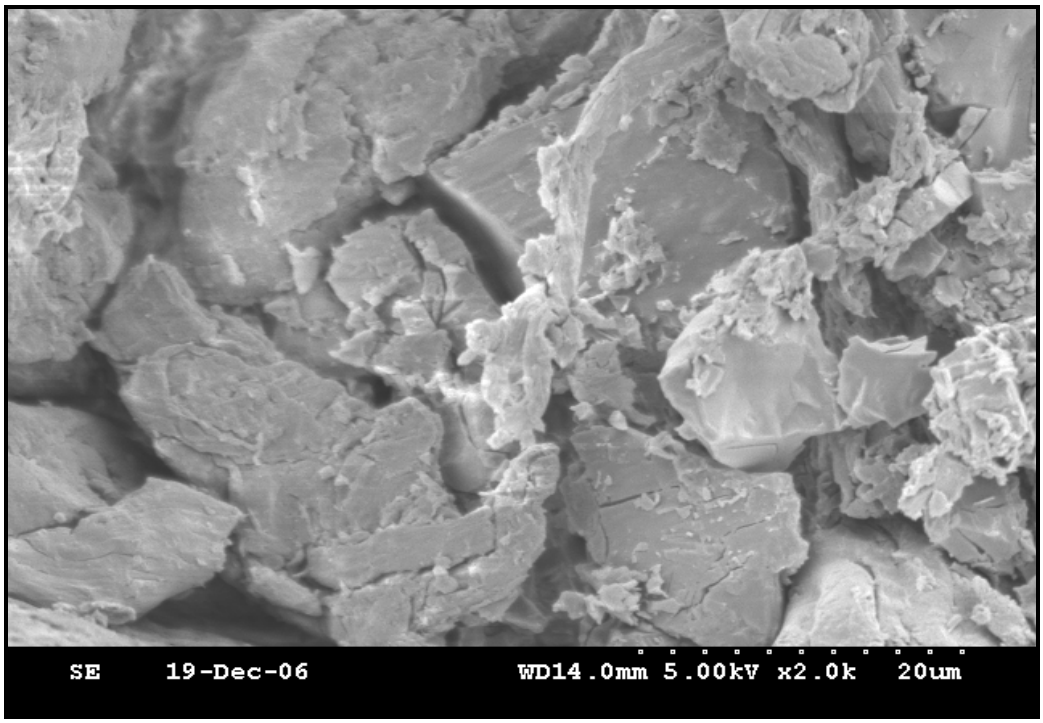

Figure 4.16. SEM images of the fracture surface of round blank Xanthan Gum tablets with porosity of 15% (magn. 2000X).

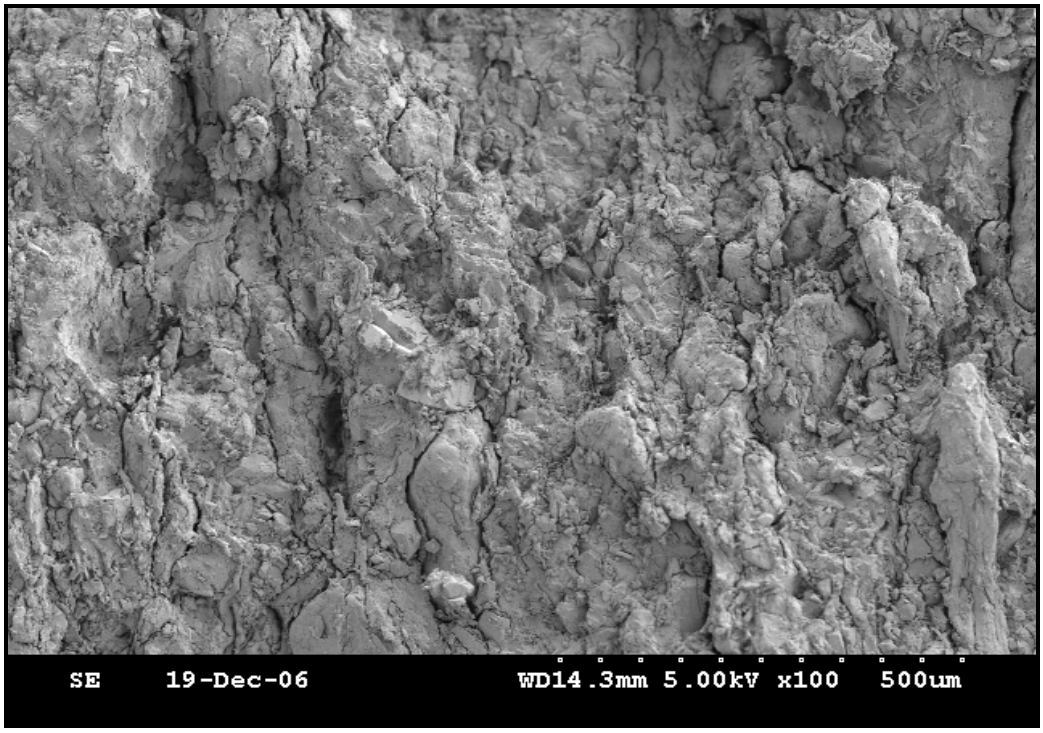

Figure 4.17. SEM images of the fracture surface of round Orphenadrine Citrate tablets with porosity of 15% (magn. 100X).

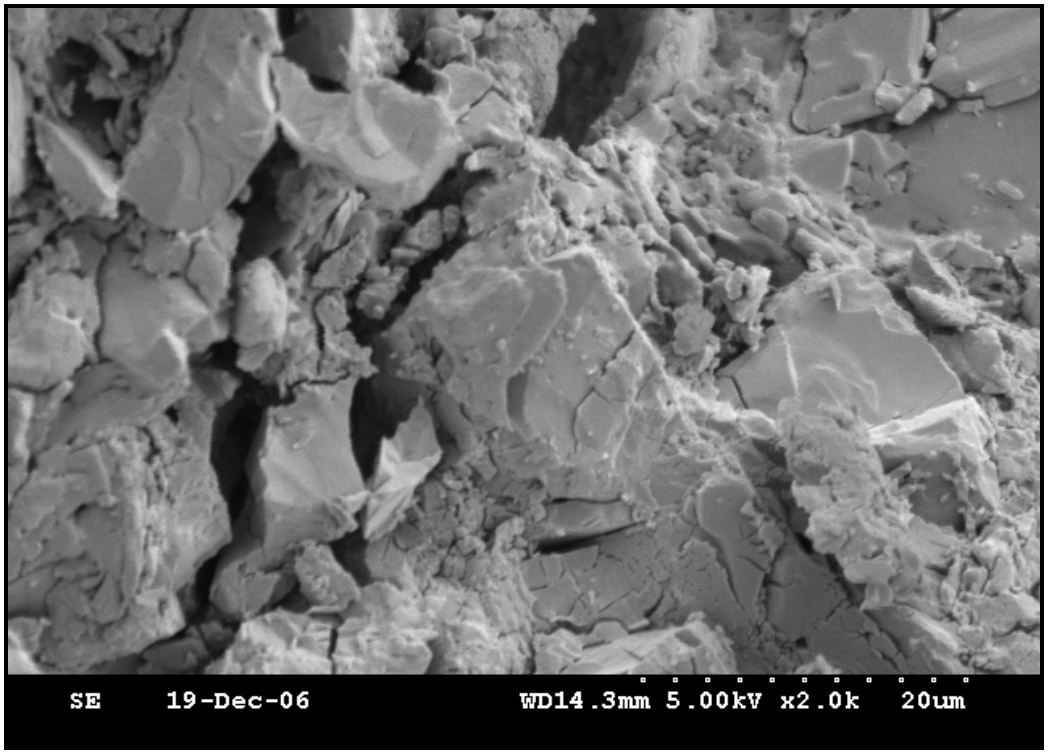

Figure 4.18. SEM images of the fracture surface of round Orphenadrine Citrate tablets with porosity of 15% (magn. 2000X).

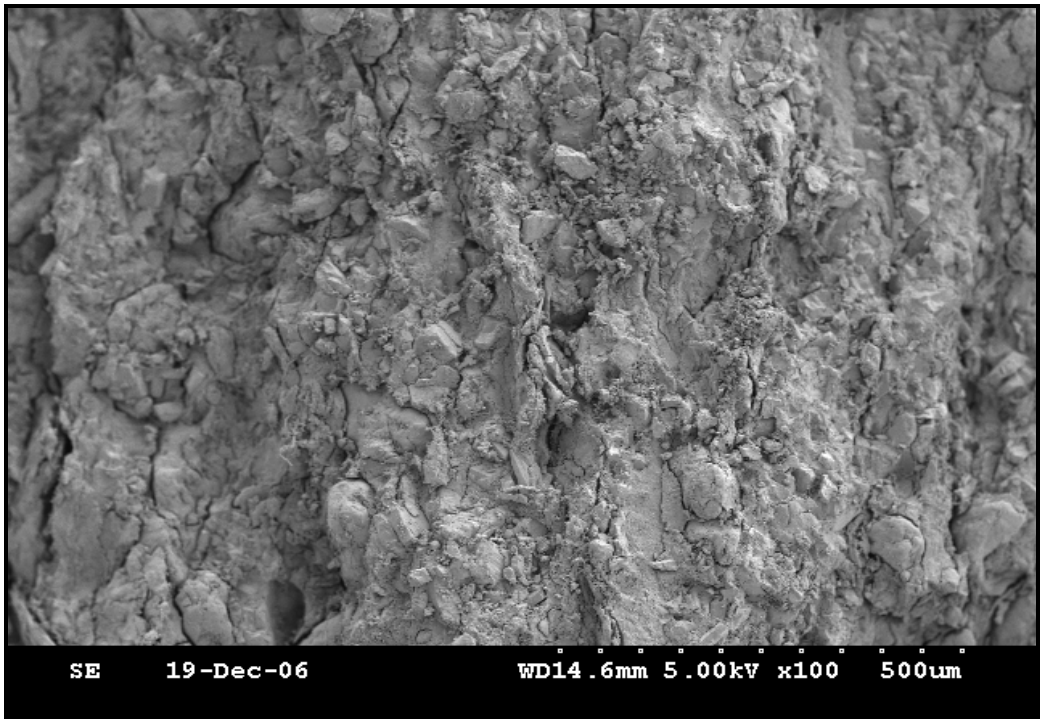

Figure 4.19. SEM images of the fracture surface of round Orphenadrine HCl tablets with porosity of 15% (magn. 100X).

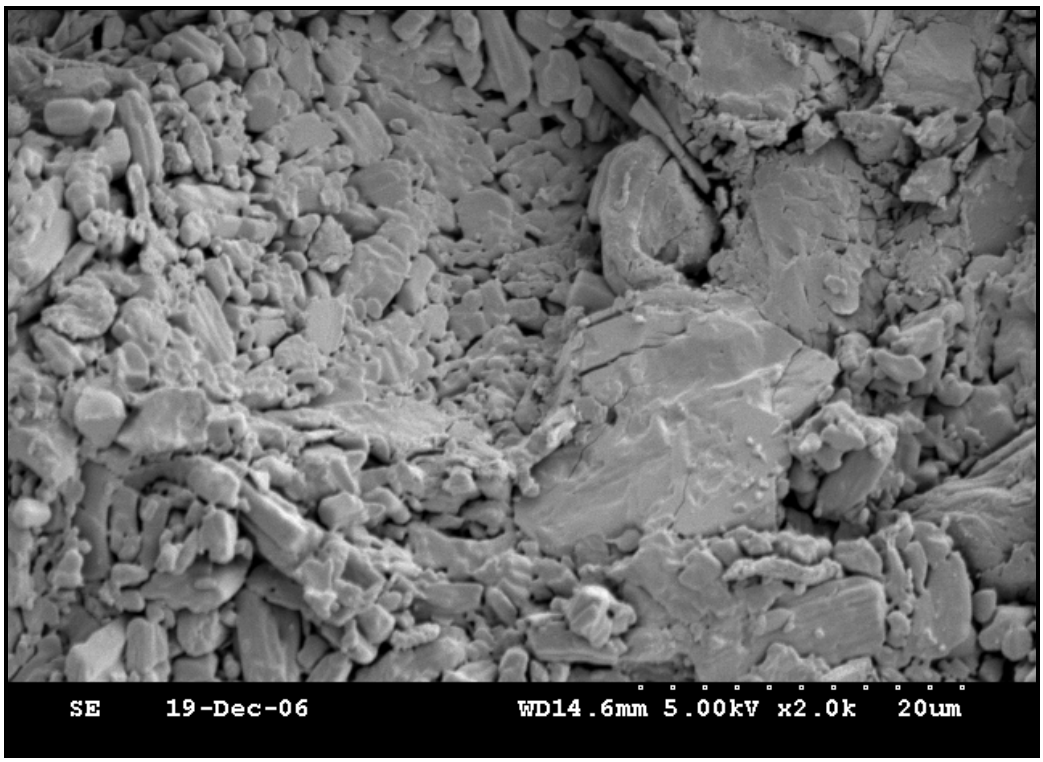

Figure 4.20. SEM images of the fracture surface of round Orphenadrine HCl tablets with porosity of 15% (magn. 2000X).

4.5. General discussion and conclusions:

The results of this chapter gave an insight into the influence of variables associated with the dosage form and with the physicochemical properties of the drugs, on the mechanical properties of hydrophilic matrix tablets. Changes in tablet shape and tablet overall porosity had a significant influence on tablet tensile strength values. This was attributed mainly to changes in the internal structure of the tablet, i.e. due to variation in the density distribution within the different tablets, and the possibility of crack formation after the compaction process. Such changes in tablet structural properties, could have a clear influence on the process of water ingress and diffusion into hydrophilic matrix tablets, and subsequently affect the swelling and expansion of such tablets.

The nature of the previously mentioned influences, which are caused by the change in tablet properties, varied among the three different formulations used in the production of tablets. This outcome was further clarified by scanning electron microscopy, which indicated a clear difference in the internal structural features, between tablets produced using the three formulations. Differences were also apparent in the external surface features of the tablets. This in turn could influence the initial hydration and drug release behaviour associated with the tablets.

CHAPTER FIVE

5. Tablet hydration studies

5.1. Introduction:

Monitoring the hydration patterns associated with hydrophilic matrix tablets constitutes an indispensable part in the investigation of such tablets. The hydration of hydrophilic matrix tablets leads to the activation of multiple processes that are crucial in their overall function. Most importantly is the formation of the gel layer on the outer surface of the tablet, this is due to the relaxation and swelling of the polymer chains upon contact with the hydration medium. The gel layer forms the main barrier to water ingress into the tablet, and subsequently drug release from within it. However, other changes may also occur within the internal structure of the tablet upon introduction into the hydration medium, such as the expansion of the dry core of the tablet. These changes may affect the overall function and integrity of the tablet.

It was thus the objective of this part of the work to thoroughly investigate the hydration patterns associated with the various tablets used in this

study. The initial objective is to compare the influence of formulation change on the hydration behaviour of the various hydrophilic matrix tablets under study.

Furthermore, the results obtained in chapter four of this study indicated that the variables associated with the dosage form; i.e. tablet, have a major influence on the physical properties of the dry tablet. This was attributed to the change in the internal structural properties of the tablet, caused by the variation in tablet face curvature and overall porosity. It was hence a further objective of this part of the work to monitor the influence of such variables on the hydration behaviour of the investigated tablets, and to observe any influence they may have on the structural properties and integrity of the tablets during the hydration process.

5.2. Choice of swelling investigation method:

As previously discussed in chapter one, several methods have been reported in the literature as techniques to investigate the swelling of hydrophilic matrix tablets. In this study it was decided to monitor the dimensional expansion of the different tablets using image analysis. Such technique provided an advantage of providing the ability to monitor the expansion of the tablets in the different directions. Moreover it allowed the investigation and comparison of the influence of the studied variables, in terms of dosage form and formulation properties, on the various dimensional changes occurring within the different tablets. This type of investigation and comparison was highly desired in our study, as the

changes in tablet properties, especially the change of tablet face curvature ratio, may cause a change in the internal structure of the tablet. It was thus important to investigate the influence of such change on the expansion of the tablets in the various directions. Another advantage of such technique is the ability to investigate the hydration of the tablets intensively and in-situ, thus eliminating any artefacts that may be caused by the extraction of the tablets from the hydration medium prior to the imaging process.

The results are reported in the form of the percentage swelling indices of the tablets in the various dimensions. Such values would relate the hydration dimensions of the various tablets to their dry state dimensions (values reported in the appendix), thus giving a clear indication of the extent of tablet hydration and expansion. Moreover, the normalisation of the dimensional values of the tablets is required if tablets with different dimensions in the dry state are to be compred.

5.3. Results and Discussion:

5.3.1. Hydration of Round tablets:

5.3.1.1. Axial swelling studies:

The axial swelling profiles of blank and drug containing round Xanthan Gum tablets with all four degrees of tablet face curvature ratio are presented in Figures 5.1 to 5.3 respectively. The swelling profiles of tablets produced at the three levels of tablet overall porosity were highly

super-imposable, thus only the profiles for tablets with overall porosity of 12.5% are presented in the figures for clarity. A detailed list of the swelling profiles of all other tablets is presented in the appendix.
For blank round Xanthan Gum tablets (Figure 5.1), immediate tablet hydration was initiated upon introduction of all tablets into the hydration medium. A uniform gel layer was clearly apparent within the first five minutes of tablet hydration. Tablet swelling was very rapid in the initial phase of hydration and gradually slowed down with progressive hydration. Such observations can be attributed to the progressive nature of gel layer formation on the outer surface of the tablets. Progressive polymer hydration leads to the thickening of the gel layer which forms a barrier to further water ingress into the dosage form, thus slowing down the process of tablet swelling. Another aspect of tablet overall expansion in the initial phase of hydration could be correlated with the expansion of the dry core within the tablet structure upon introduction into the hydration medium. Such observations were previously examined within tablets produced with HPMC using nuclear magnetic imaging. They were attributed to the relaxation of the stresses within the tablet structure upon hydration (Rajabi-siahboomi et al 1994).

A clear change in tablet hydration behaviour was caused upon introduction of either of the two model drugs used in this study. For tablets containing the drug Orphenadrine Citrate (Figure 5.2), the hydration process was initiated with a very rapid and marked erosion process, which was visually apparent. However, within the first ten

minutes of tablet hydration, a uniform gel layer was clearly visible on the surface of the tablets. Tablet swelling was rapid in the initial hydration phase and slowed down with progressive hydration. In comparison with blank Xanthan Gum tablets, the swelling of tablets containing the drug Orphenadrine Citrate was much slower. This could be indicative of the diminished ability of the polymer chains to fully hydrate and swell.

The addition of the drug Orphenadrine HCl seems to have had the most detrimental influence on table swelling. The axial swelling profiles of such tablets are presented in Figure 5.3. Upon introduction into the hydration medium these tablets exhibited a marked and prolonged erosion process. Only a highly irregular gel layer was apparent on the surface of such tablets within the first two hours of hydration. Moreover, crack formation was apparent within the gel layer on the sides of such tablets. Cracks were noted on the sides of tablets with all four degrees of face curvature ratio. However, the extent of crack formation and enlargement progressively increased with the increase in tablet face curvature ratio; clearly visible deep cracks were formed on the sides of tablets with face curvature degrees of 1 and 1.43. Such behaviour could be highly correlated with the previously discussed process of tablet core expansion; the gel layer formed within tablets containing the drug Orphenadrine HCl seems to be too weak to withstand any potential expansion of the dry core of the tablet upon introduction into the hydration medium. The extent of any potential expansion in the dry core of the hydrating tablets would be greater in tablets with higher degrees of face curvature ratio due to the

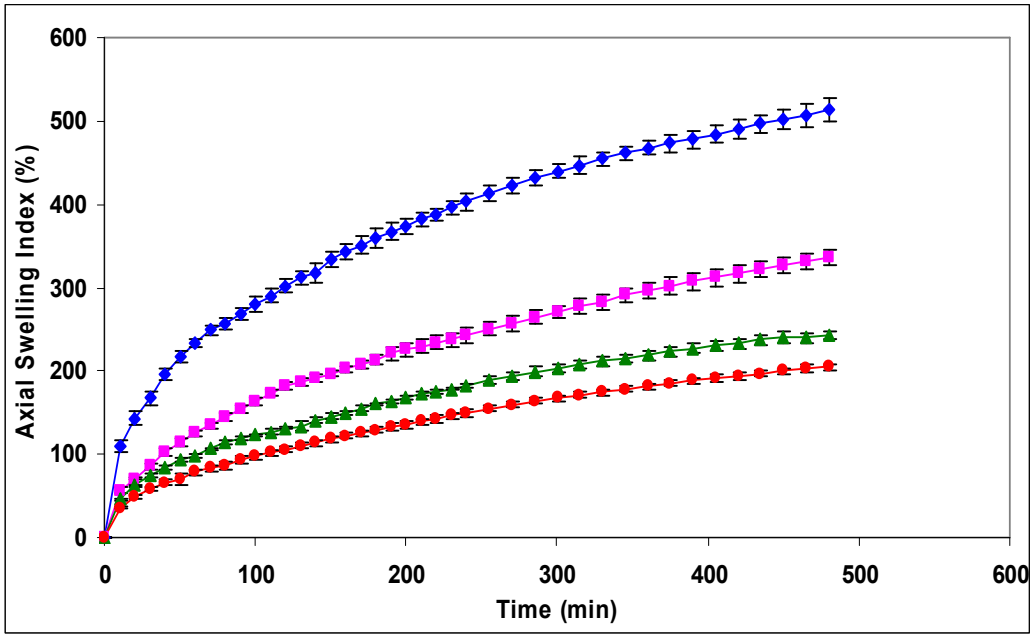

Figure 5.1. Axial swelling profiles of round blank Xanthan Gum tablets, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

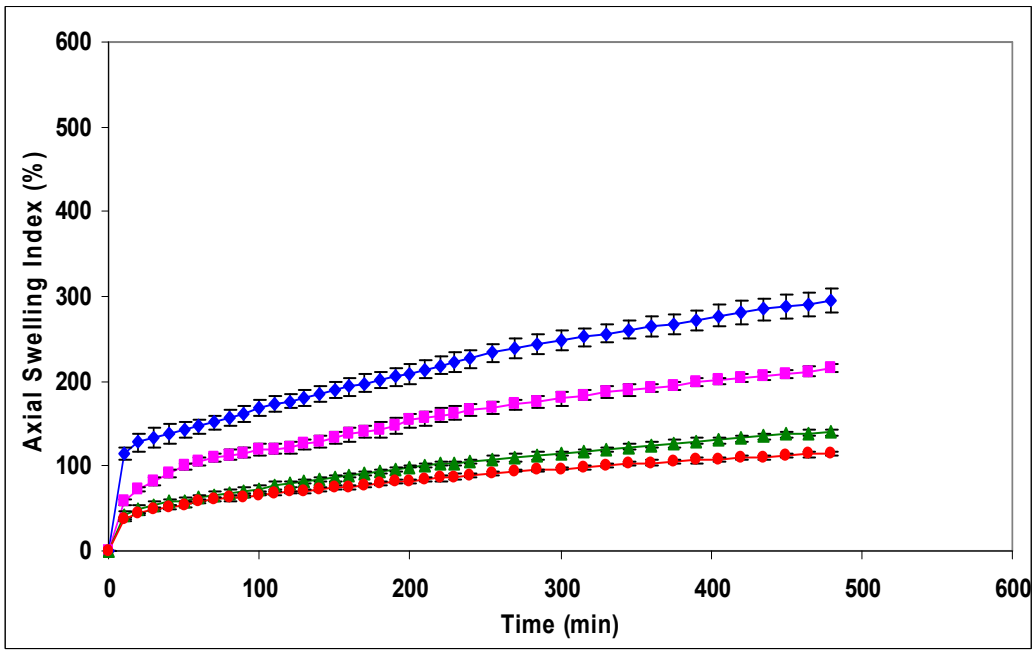

Figure 5.2. Axial swelling profiles of round Xanthan Gum tablets with Orphenadrine Citrate, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

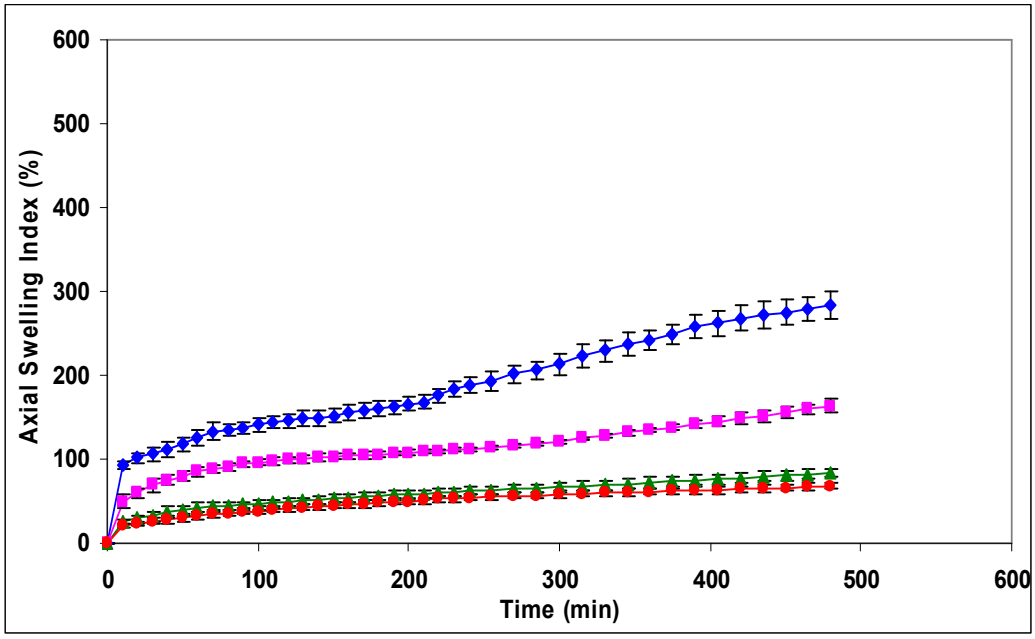

Figure 5.3. Axial swelling profiles of round Xanthan Gum tablets with Orphenadrine HCl, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

higher densification process occurring within the edges of such tablets during compaction. Crack formation was also evident in tablets produced at al three levels of tablet overall porosity. No differences were observed between tablets produced at al three porosities.

Upon further hydration of all tablets containing the drug Orphenadrine HCl, a gradual formation of a uniform gel layer was apparent on the surface of the tablets, and within the cracks formed on the sides of such tablets, leading to the enhancement of tablet swelling. Such behaviour was more marked in tablets with the lower degrees of face curvature ratio of 0 and 0.5 in which tablet swelling became much faster with progressive hydration. This pattern of tablet swelling behaviour indicates that

progressive release of the drug from the internal environment of the tablet seemed to restore the ability of the polymer to hydrate freely.

5.3.1.2. Statistical comparison of the axial swelling profiles of round tablets:

An intensive technique was required to compare the swelling profiles of the tablets used in this study due to the multiple number of variables affecting the swelling behaviour of the tablets, and due to the complex hydration patterns associated with such tablets, especially those tablets containing the drug Orphenadrine HCl, in which the extent of tablet swelling was clearly different during the various phases of the hydration process. Such hydration patterns make it inappropriate to represent the whole hydration process in single numerical parameters. A combined statistical approach was used to gain thorough understanding of the swelling patterns associated with the studied tablets, and to compare such behaviour between the different tablets. The method comprised of the use of analysis of variance (ANOVA), which was previously discussed in Chapter 4, in addition to multivariate analysis of variance (MANOVA).

Multivariate analysis of Variance (MANOVA) could be regarded as an extension of the previously discussed ANOVA (Chapter 4). MANOVA adopts a similar analysis method to ANOVA. However, the main difference is the presence of two or more dependent variables under investigation, in contrast to the single dependent variable investigated in ANOVA. MANOVA requires the presence of some kind of relationship

between the multiple dependent variables, and it adopts the principle of matrix algebra as a numerical basis for calculations (Podczeck 2003). It could thus be seen that a potential practical advantage of MANOVA over ANOVA is its ability to investigate the entire range of dependent variables under investigation simultaneously. In this study these are the multiple swelling indices of the tablets. Thus MANOVA could facilitate the comparison of the entire swelling profiles of the tablets.

Observing the axial swelling patterns associated with the tablets produced using the different formulations (Figures 5.1. to 5.3.) makes it evident that changing the type of formulation used in the production of the different tablets has a major effect on their axial swelling. Thus, and in order to investigate the influence of dosage form variables in terms of face curvature and overall porosity on the hydration patterns of tablets, and to compare any changes in such influence upon changing tablet formulation, statistical analysis was carried out for each of the three formulations separately.

Initially MANOVA was employed to investigate the influence of tablet face curvature ratio and tablet overall porosity on the whole swelling profile. Then multiple ANOVAs were carried out at different time points representing the different phases of tablet swelling, in order to further elucidate the results of the MANOVA investigation, and to investigate the influence of tablet face curvature ratio and overall porosity on tablet swelling, and possible changes in such influence with time.

MANOVA results for the axial swelling profiles of tablets produced using the three different formulations are listed in Tablet 5.1. Upon investigating the influence of tablet face curvature and overall porosity on the overall axial swelling of blank round Xanthan Gum tablets, it becomes apparent that the degree of tablet face curvature is the only variable with significant influence on tablet overall axial swelling; with a Hotelling's trace value of 1127.901, (approximated F value of 184.850) corresponding to a p value of less than 0.001. The influence of tablet overall porosity, and that of the interaction between the degree of tablet face curvature and tablet overall porosity on tablet overall axial swelling are not significant as their p values are considerably higher than the set significance level of 0.05. A similar pattern is observed with tablets containing the drug Orpneadrine Citrate, in which the degree of tablet face curvature is the only factor with significant influence on tablet overall axial swelling with a Hotelling's trace value of 634.948, (approximated F value of 104.061) corresponding to a p value of less than 0.001.

A somewhat different result is noted with tablets containing the drug Orphenadrine HCL, as the MANOVA results for such tablets show a significant influence on tablet overall axial swelling associated with both dosage form variables; i.e. tablet face curvature ratio and tablet overall porosity with significance values lower than the set value of 0.05. Moreover the interaction between both factors seems to have a significant influence on tablet overall axial swelling. However, upon comparing the F values associated with the three variables, it becomes

clear that the main variable influencing tablet swelling is the ratio of tablet face curvature with an F value of 126.939; this value is considerably higher than the F values associated with tablet overall porosity and the interaction between the tablet face curvature ratio and overall porosity, which were 2.342 and 1.400 respectively. It could thus be concluded that although the influence of these two variables on tablet overall axial swelling is significant, the swelling process as such is dominated by the tablet face curvature ratio.

Tablet type	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Blank	Porosity	3.900	0.975	80.000	40.000	0.549
	Curvature	1127.901	184.850	120.000	59.000	< 0.001
	Porosity*Curvature	9.106	0.734	240.000	116.000	0.976
Citrate	Porosity	5.403	1.351	80.000	40.000	0.149
	Curvature	634.948	104.061	120.000	59.000	< 0.001
	Porosity*Curvature	12.102	0.975	240.000	116.000	0.570
HCl	Porosity	9.367	2.342	80.000	40.000	0.002
	Curvature	774.541	126.939	120.000	59.000	< 0.001
	Porosity*Curvature	17.377	1.400	240.000	116.000	0.021

Table 5.1. MANOVA results for the axial swelling of round Xanthan Gum tablets.

The results of the two -way ANOVA investigation for blank round Xanthan Gum tablets are presented in Table 5.2. The results clearly indicate that the only variable with significant influence on tablet axial hydration at the three chosen time points is the ratio of tablet face curvature as noted from the significance values which are consistently lower that the set p value of 0.05.

Further insight into the differences between the different degrees of tablet face curvature ratio was accomplished by the use of the post hoc Sheffé test, the use of which was justified due to the significance associated with this variable. As previously mentioned in chapter four, the output of the Sheffé test arranges the different levels of the studied variable in progressively increasing subsets. The values falling within the same subset are statistically similar and at the same time significantly different from the values falling into other subsets. The results of the Sheffé test for blank Xanthan Gum tablets indicated that at all three time points there was a significant difference between all four degrees of tablet face curvature ratio. The highest axial swelling was consistently associated with flat tablets with a face curvature ratio of 0 and it became progressively and significantly lower with the progressive increase in tablet face curvature ratio. A list of the Sheffé test results obtained with the different tablets is reported in the appendix.

The results of the two -way ANOVA investigation for tablets containing the two drugs are presented in Tables 5.3. and 5.4 respectively. The results for tablets containing both drugs are similar to those obtained with the blank tablets in which tablet face curvature ratio is the only variable with significant influence on the axial swelling of tablets at the three time points investigated.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.067	0.935
	Curvature	3	4279.126	< 0.001
	Porosity*Curvature	6	0.767	0.599
240	Porosity	2	0.483	0.619
	Curvature	3	3908.144	< 0.001
	Porosity*Curvature	6	0.365	0.898
480	Porosity	2	0.084	0.919
	Curvature	3	3741.397	< 0.001
	Porosity*Curvature	6	0.124	0.993

Table 5.2. Two -way ANOVA results for the axial swelling of round blank Xanthan Gum tablets.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.142	0.868
	Curvature	3	960.009	< 0.001
	Porosity*Curvature	6	0.156	0.987
240	Porosity	2	0.092	0.913
	Curvature	3	1244.918	< 0.001
	Porosity*Curvature	6	0.055	0.999
480	Porosity	2	0.200	0.820
	Curvature	3	1940.624	< 0.001
	Porosity*Curvature	6	0.282	0.943

Table 5.3. Two -way ANOVA results for the axial swelling of round Xanthan Gum tablets with Orphenadrine Citrate.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.290	0.750
	Curvature	3	1093.480	< 0.001
	Porosity*Curvature	6	1.039	0.409
240	Porosity	2	0.166	0.847
	Curvature	3	1221.310	< 0.001
	Porosity*Curvature	6	2.003	0.079
480	Porosity	2	0.293	0.747
	Curvature	3	1703.988	< 0.001
	Porosity*Curvature	6	0.208	0.973

Table 5.4. Two -way ANOVA results for the axial swelling of round Xanthan Gum tablets with Orphenadrine HCl.

Post hoc analysis for the significant variable “tablet face curvature ratio” for both drugs indicated a pattern similar to that observed with blank tablets. A significant influence was noted between all four degrees of tablet face curvature ratio at al three time points investigated. The highest axial swelling was noted with flat tablets with a face curvature ratio of 0, and the values progressively and significantly decreased with the increase in tablet face curvature ratio.

The two -way ANOVA results for tablets containing the drug Orphenadrine HCl indicated that there was no significant influence on tablet axial swelling associated with tablet overall porosity and the interaction product at al three time points investigated. However, the results for the MANOVA investigation conducted on the same tablets indicated a somewhat significant influence associated with these variables. Two factors should be taken into consideration upon comparing

such results. Initially, MANOVA investigates the overall swelling profile rather than single time points. More importantly, and as noted previously in Table 5.1., the magnitude of the influence associated with these two variables are much smaller than that associated with tablet face curvature ratio. Thus it could be concluded that the influence of tablet overall porosity on the axial swelling of such tablets is rather marginal.

5.3.1.3. Radial swelling studies:

The radial swelling profiles of blank and drug containing round Xanthan Gum tablets with all four degrees of face curvature ratio and an overall porosity of 12.5% are presented in Figures 5.4 to 5.6., respectively. Upon comparing the swelling profiles of blank and drug containing tablets, a pattern similar to that observed with the axial swelling profiles of the tablets was found. Blank Xanthan Gum tablets (Figure 5.4.) exhibited a gradual swelling process with the formation of a uniform gel layer on the surface of the tablet. The swelling of such tablets was more pronounced in the initial phase of tablet hydration.

Upon introduction of either of the two model drugs used in the study a clear drop in the swelling ability of all tablets was observed. Tablets containing the drug Orphenadrine Citrate (Figure 5.5.) exhibited a rapid erosion process, followed by the formation of a uniform gel layer, and progressive tablet swelling, at a slower rate in comparison with blank tablets. Tablets containing the drug Orphenadrine HCl (Figure 5.6.) underwent prolonged erosion immediately after introduction into the

hydration medium with the formation of an irregular gel layer on the surface. Crack formation was apparent on the radial faces of tablets with all four degrees of face curvature ratios and all degrees of tablet overall porosity. However, the extent of crack formation and propagation on the radial faces of all tablets was less evident than that observed on the axial sides of the tablets. Moreover, an increase in the swelling ability of the tablets was apparent in the later stages of the hydration process, in a manner similar to that observed during the axial swelling studies. This was particularly evident within flat tablets in which drug release is expected to be faster. This is due to the smaller size of such tablets which results in faster hydration and drug release, resulting in the enhanced ability of the polymer to hydrate and swell.

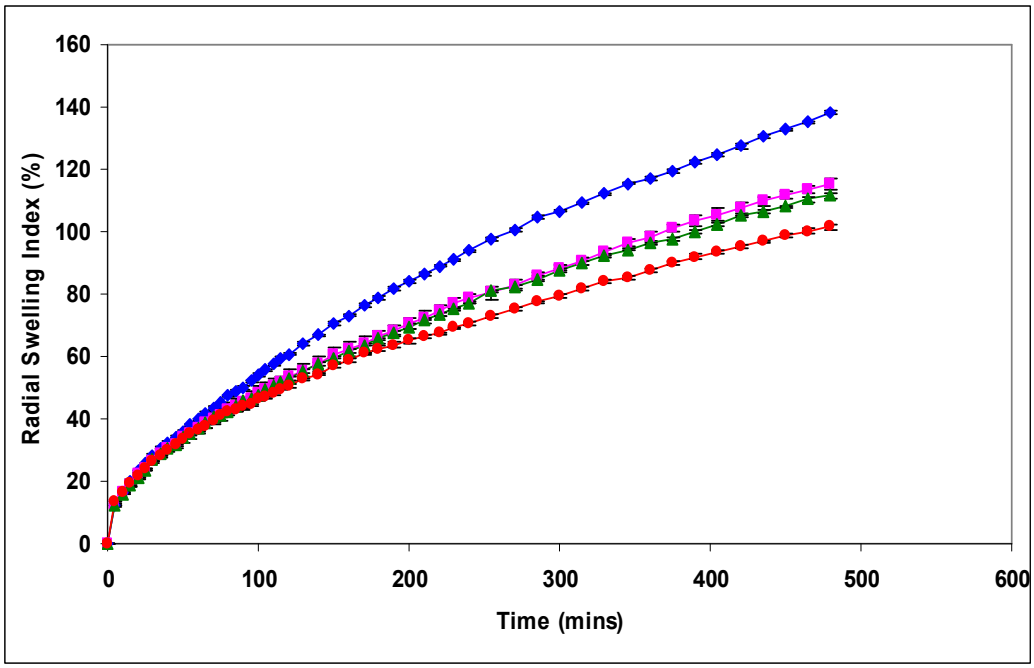

Figure 5.4. Radial swelling profiles of round blank Xanthan Gum tablets, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

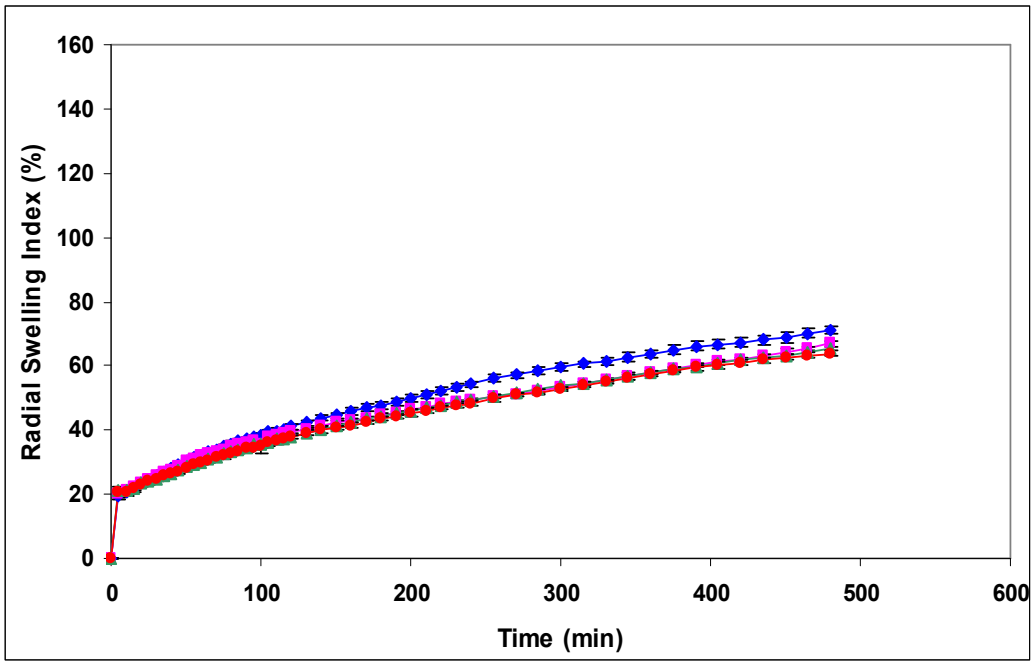

Figure 5.5. Radial swelling profiles of round Xanthan Gum tablets with Orphenadrine Citrate, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

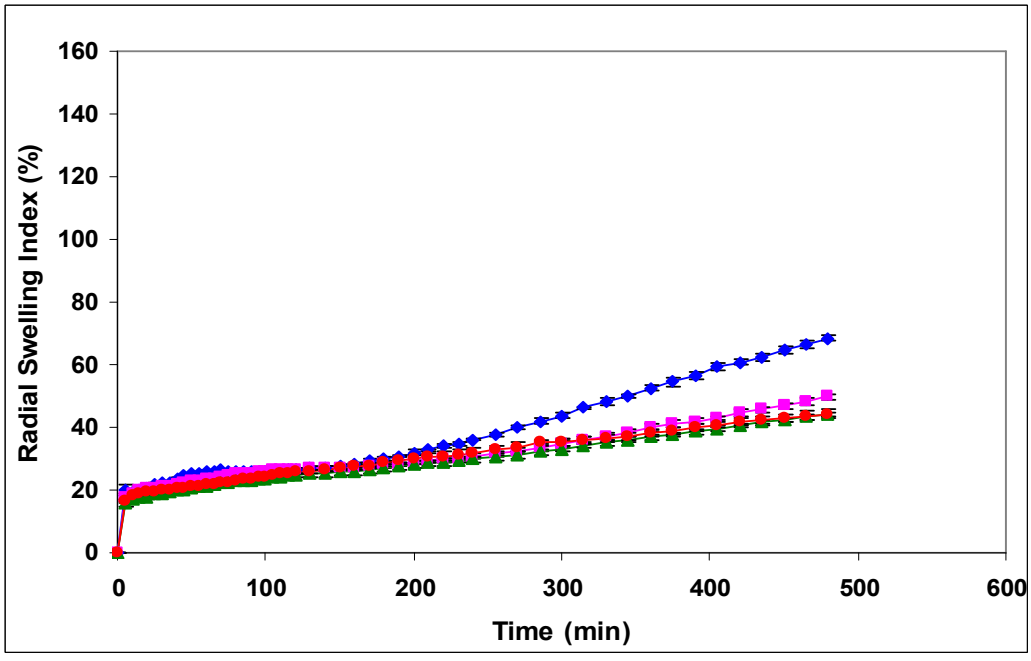

Figure 5.6. Radial swelling profiles of round Xanthan Gum tablets with Orphenadrine HCl, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

5.3.1.4. Statistical comparison of the radial swelling profiles of round tablets:

The results for the MANOVA investigation of the overall radial swelling of blank and drug containing round Xanthan Gum tablets are presented in Table 5.5. They indicate a more complex process in comparison to the axial swelling of the tablets. A similar pattern is noted with all three types of tablets in which both dosage form associated variables; i.e. tablet face curvature ratio and tablet overall porosity seem to have a significant influence on the overall radial swelling of tablets which is indicated by their p values which are consistently lower than the threshold value of 0.05. Moreover, the interaction between the two variables is also significant for all three types of tablets, and this indicates that the influence caused by one of the two variables is different at the different levels of the other variable.

However, upon comparison of the F values associated with both variables and their interaction product, it becomes clearly evident that the F values associated with the tablet face curvature ratio are consistently and considerably higher than those associated with tablet overall porosity and the interaction product between both variables. This is indicating that tablet face curvature ratio is the main factor affecting the overall tablet radial swelling with minor influence caused by the change in tablet porosity.

Tablet type	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Blank	Porosity	57.312	4.409	104.000	16.000	0.001
	Curvature	2904.465	142.741	156.000	23.000	< 0.001
	Porosity*Curvature	140.842	3.310	312.000	44.000	< 0.001
Citrate	Porosity	47.837	3.680	104.000	16.000	0.002
	Curvature	411.942	20.245	156.000	23.000	< 0.001
	Porosity*Curvature	182.928	4.300	312.000	44.000	< 0.001
HCl	Porosity	35.361	2.720	104.000	16.000	0.013
	Curvature	2340.954	115.047	156.000	23.000	< 0.001
	Porosity*Curvature	126.379	2.970	312.000	44.000	< 0.001

Table 5.5. MANOVA results for the radial swelling of round Xanthan Gum tablets.

Further investigation of the radial swelling behaviour of all tablets at the different time intervals was accomplished using multiple two-way ANOVA investigations, the results of which are presented in Tables 5.6. to 5.8. The results for round blank Xanthan Gum tablets (Table 5.6.) indicate that both dosage form variables have a significant influence on the radial swelling of blank tablets at all three time points. Moreover, the interaction between both variables also has a significant influence on tablet radial swelling. However, and as noted previously, the effect of tablet face curvature seems to be the main factor affecting tablet swelling as indicated by the high F values, as compared to the lower F value associated with tablet overall porosity and the interaction product.

In order to elucidate the nature of the interaction between the two associated dosage form variables, follow up studies were carried out using one-way ANOVA to investigate the influence of tablet face

curvature ratio at each of the three levels of tablet overall porosity separately. As before, this was followed by post-hoc analysis using the Sheffé test to elucidate the differences between the various levels of tablet face curvature ratio. A complete list of the Sheffé test results is reported in the appendix.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	28.749	< 0.001
	Curvature	3	262.822	< 0.001
	Porosity*Curvature	6	4.760	< 0.001
240	Porosity	2	62.144	< 0.001
	Curvature	3	1711.333	< 0.001
	Porosity*Curvature	6	7.486	< 0.001
480	Porosity	2	115.826	< 0.001
	Curvature	3	4069.848	< 0.001
	Porosity*Curvature	6	10.165	< 0.001

Table 5.6. Two -way ANOVA results for the radial swelling of round blank Xanthan Gum tablets.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	3.219	0.047
	Curvature	3	72.129	< 0.001
	Porosity*Curvature	6	1.470	0.204
240	Porosity	2	5.958	0.004
	Curvature	3	131.949	< 0.001
	Porosity*Curvature	6	1.223	0.307
480	Porosity	2	2.261	0.113
	Curvature	3	220.450	< 0.001
	Porosity*Curvature	6	1.226	0.306

Table 5.7. Two -way ANOVA results for the radial swelling of round Xanthan Gum tablets with Orphenadrine Citrate.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	5.969	0.004
	Curvature	3	31.065	< 0.001
	Porosity*Curvature	6	2.557	0.028
240	Porosity	2	0.192	0.826
	Curvature	3	67.817	< 0.001
	Porosity*Curvature	6	3.371	0.006
480	Porosity	2	2.421	0.097
	Curvature	3	1184.646	< 0.001
	Porosity*Curvature	6	1.404	0.228

Table 5.8. Two -way ANOVA results for the radial swelling of round Xanthan Gum tablets with Orphenadrine HCl.

Upon comparing the different degrees of tablet face curvature it was clearly apparent that flat tablets had consistently higher swelling indices in comparison with the other tablets. Such behaviour could be attributed to the faster hydration process occurring in tablets with lower degrees of tablet face curvature ratio. The differences between tablets with higher degrees of tablet face curvature were initially smaller in magnitude, and had slight variations with the change in tablet overall porosity. With progressive hydration clear differences became apparent between the different tablets. This is evident from the increase in the F value associated with this variable with the progressive increase in time. Clear differences were apparent between all four degrees of tablet face curvature ratio at 480 minutes.

The results of the two-way ANOVA analysis for the radial swelling of round Xanthan Gum tablets with Orphenadrine Citrate (Table 5.7.) indicate a significant influence associated with tablet face curvature ratio at all three time points as indicated by the p values. The effect of tablet overall porosity seems to be significant at the first two time points only as indicated by the p values. No significant effect is noted with the interaction product between the two associated dosage form variables, which indicates the independence of the effect caused by each factor. Thus, the effect of each factor has to be interpreted separately.

The results of the Sheffé test for tablet face curvature ratio showed that, initially at 120 minutes, tablets with the two lower degrees of face curvature had similar swelling indices that were significantly higher than those associated with tablets with higher degrees of face curvature. With further hydration, tablet swelling became inversely related to the degree of tablet face curvature. Finally, clear differences were noted between all four degrees of tablet face curvature ratio at 480 minutes. A similar pattern to that noted with blank tablets is observed with the time dependent increase in the F value associated with the degree of tablet face curvature ratio.

In terms of tablet porosity, the use of the Sheffé test was only justified at the two initial time points due to the significance level associated with this variable at these two points. Initially at 120 minutes, the only significant difference was noted between tablets with an overall porosity of 17.5%

and those with an overall porosity of 12.5%, with the former having higher radial swelling indices. At 240 minutes the radial swelling indices of tablets with an overall porosity of 17.5% were significantly higher than those associated with tablet produced at the two lower levels of overall porosity of 12.5% and 15% which were statistically similar.

The results of the two-way ANOVA investigation of round Xanthan Gum tablets with Orphenadrine HCl (Table 5.8.) indicate a more complex and time dependent pattern. Initially at 120 minutes both associated dosage form variables seem to have a significant influence on the radial swelling of the tablets in addition to a significant influence caused by the interaction product of both variables. At 240 minutes only the degree of tablet face curvature ratio seems to have a significant effect on tablet radial swelling. However, the interaction between this variable and tablet overall porosity is also significant. At 480 minutes the only significant influence factor is the degree of tablet face curvature ratio.

Once again one-way ANOVA investigations were carried out at each level of tablet overall porosity when the interaction product between the two dosage form associated variables was significant. Moreover post hoc analysis using the Sheffé test was carried out for the degree of face curvature ratio. Initially, slight variation in the radial swelling indices of tablets with the four degrees of face curvature was noted. Furthermore, small differences were observed between tablets having different overall porosities. The differences between the radial swelling indices of the

tablets increased progressively with time. This is clearly evident from the increase of the in the F value.

Ultimately at 480 minutes the results of the Sheffé test indicated the presence of three different subsets, the highest of which contained the mean radial swelling index of flat tablets. The middle subset contained the mean radial swelling index of tablets with a face curvature ratio of 0.5. The lowest subset contained the mean swelling indices of tablets with face curvature ratios of 1 and 1.43. The lack of significant difference between the swelling indices of tablets with the two higher degrees of tablet face curvature could be highly correlated with the previously noted crack formation which was much more evident in highly convex tablets with a face curvature ratio of 1.43. Such behaviour could have led to extensive water penetration into the internal structure of the tablets leading to an increase in the rate of tablet hydration.

Upon close observation of the swelling profiles associated with the different tablets (Figures 5.1 to 5.3) and (Figures 5.4. to 5.6.), it becomes evident that the differences between the swelling profiles of tablets produced at the different degrees of face curvature became less pronounced upon inclusion of either of the two model drugs used in this study. Such behaviour is also evident upon comparing the F values associated with tablet face curvature ratio that were obtained during the various statistical investigations; the F values obtained with blank tablets are consistently higher than those obtained with either drugs indicating a

more pronounce influence of this factor on the swelling patterns of blank Xanthan Gum tablets in comparison to drug containing tablets.

5.3.2. Hydration of elongated tablets:

5.3.2.1. Height swelling studies:

The results for the height swelling investigation of blank and drug containing elongated Xanthan Gum tablets are presented in the form of their time dependent swelling profiles (Figures 5.7. to 5.9.). A pattern similar to that obtained with the axial swelling studies conducted on round tablets can be observed; for blank elongated Xanthan Gum tablets (Figure 5.7.) a steady swelling process was initiated immediately after introducing the tablets into the hydration medium. The overall expansion process was faster in the early stages of tablet hydration and slowed down progressively with time. Such behaviour could be associated with the reasons previously mentioned in section 5.3.1.1. of this chapter; i.e. the progressive thickening of the gel layer and its retarding effect on water penetration, and the possible expansion of the dry tablet core in the early stages of hydration.

Tablets containing the drug Orphenadrine Citrate (Figure 5.8.) exhibited a slow and steady swelling process which was initiated after a short erosion process. However, elongated Xanthan Gum tablets containing the drug Orphenadine HCl (Figure 5.9.) underwent a profound and lengthy erosion process initially. With progressive hydration, a steady formation of a

uniform gel layer was observed in these tablets. This later behaviour was more profound in flat tablets which underwent significant swelling in the later stages of the hydration process.

Crack formation, which was a noticeable in round Xanthan Gum tablets with Orphenadrine HCl, was also clearly visible in elongated tablets with the same drug; this behaviour was also more profound in the early hydration stages and in tablets with higher face curvature degrees, in which larger cracks were formed.

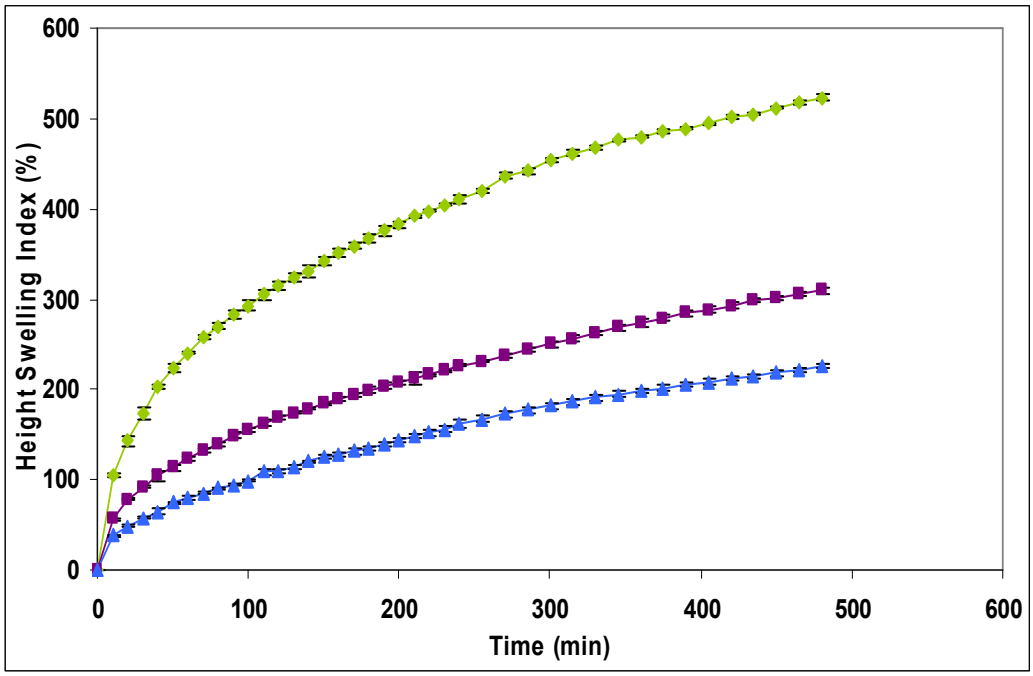

Figure 5.7. Height swelling profiles of elongated blank Xanthan Gum tablets, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲- (curvature 2 mm), (n=3).

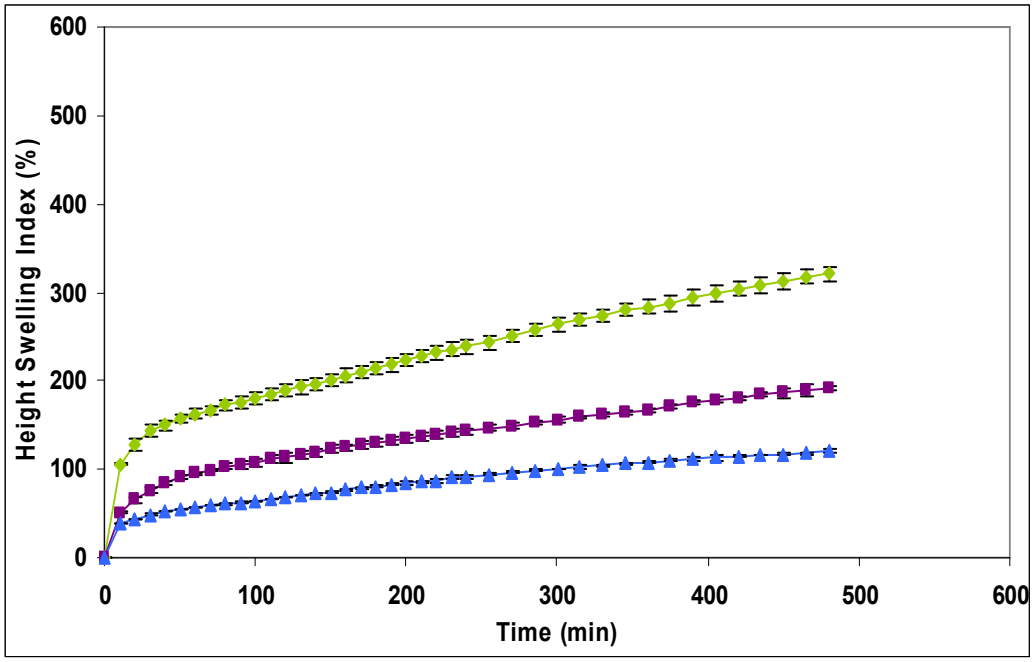

Figure 5.8. Height swelling profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

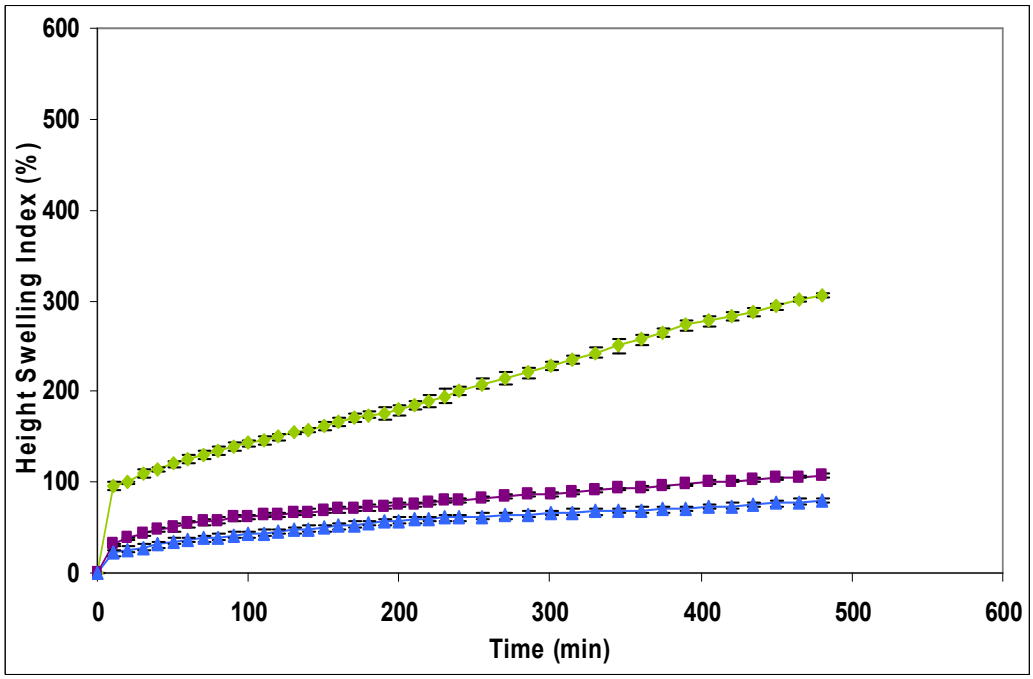

Figure 5.9. Height swelling profiles of elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

5.3.2.2. Statistical comparison of the height swelling profiles of elongated tablets:

The statistical comparison of the various swelling profiles investigated during the hydration of blank and drug containing Xanthan Gum elongated tablets was accomplished using the use of analysis of variance (ANOVA) at three time points within the swelling profile. In a manner similar to that conducted in the investigation of round tablets, the three time points were chosen to represent the progressive hydration stages of the tablets. The use of multivariate analysis of variance (MANOVA) in the statistical comparison of the swelling profiles of elongated tablets was not feasible. Such observation could be explained in terms of the properties of these statistical methods. Two of the assumptions usually required for both univariate and multivariate techniques for the analysis of variance are normal distribution of the observations and variance homogeneity between the studied samples. As it was discussed in Chapter 4, the F ratio employed by ANOVA is robust to small deviations in the requirement of variance homogeneity, particularly when the size of the studied samples is equal (Stevens 1996). In the case of MANOVA, there is also a certain robustness of the statistical parameters to small violations of the assumptions. However, other factors can exacerbate such effects, mainly, the larger number of dependent variables studied together, and the actual size of the studied samples in relation to the number of the dependent variables studied, which was smaller in the case of elongated tablets. Thus, the use of ANOVA at multiple time points within the

swelling profiles was regarded as a preferred and more robust technique for the investigation of the swelling behaviour of such tablets.

The results of the two-way ANOVA investigations conducted on the height swelling profiles of the various elongated tablets at the three time points of 120, 240 and 480 minutes are presented in Tables 5.9. to 5.11.. A similar pattern is observed with tablets produced using all three formulations; the only factor to have a significant influence on the height swelling process of the tablets is the degree of tablet face curvature. This is clearly noticeable by observing the F ratios associated with this factor and the corresponding p values which are consistently lower that the significance threshold value of 0.05. On the other hand, the influence associated with tablet overall porosity is clearly not significant at all three time points and this is indicated by the p values associated with this factor which are considerably higher than the threshold of 0.05. A similar trend of lack of significance is also associated with the interaction product between tablet face curvature and overall porosity. It could be thus concluded that for elongated Xanthan Gum tablets used in this study, the only factor influencing the height swelling process is the degree of tablet face curvature.

To clarify the differences between the different degrees of tablet face curvature, and in a similar manner to that conducted with round tablets, post hoc Sheffé analysis was conducted for tablets produced using each of the three formulations separately. A similar pattern was observed with

all three formulations in which statistically significant differences were observed between all three degrees of tablet face curvature in terms of their height swelling indices. The swelling indices were highest for flat tablets and progressively and significantly decreased with the increase in tablet face curvature. A complete list of the results of the Sheffé analysis is reported in the appendix.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.071	0.931
	Curvature	2	7427.030	< 0.001
	Porosity*Curvature	4	0.559	0.696
240	Porosity	2	0.372	0.695
	Curvature	2	5765.231	< 0.001
	Porosity*Curvature	4	0.195	0.938
480	Porosity	2	0.453	0.643
	Curvature	2	16153.070	< 0.001
	Porosity*Curvature	4	0.315	0.864

Table 5.9. Two -way ANOVA results for the height swelling of elongated blank Xanthan Gum tablets.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.034	0.966
	Curvature	2	1795.489	< 0.001
	Porosity*Curvature	4	0.665	0.624
240	Porosity	2	0.023	0.978
	Curvature	2	2936.629	< 0.001
	Porosity*Curvature	4	0.458	0.765
480	Porosity	2	0.030	0.970
	Curvature	2	5100.527	< 0.001
	Porosity*Curvature	4	0.265	0.896

Table 5.10. Two -way ANOVA results for the height swelling of elongated Xanthan Gum tablets with Orphenadrine Citrate.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.188	0.830
	Curvature	2	1928.126	< 0.001
	Porosity*Curvature	4	0.732	0.582
240	Porosity	2	1.068	0.364
	Curvature	2	3044.582	< 0.001
	Porosity*Curvature	4	1.462	0.255
480	Porosity	2	0.002	0.998
	Curvature	2	17128.276	< 0.001
	Porosity*Curvature	4	0.412	0.798

Table 5.11. Two -way ANOVA results for the height swelling of elongated Xanthan Gum tablets with Orphenadrine HCl.

5.3.2.3. Width and length swelling studies:

The width and length swelling profiles for blank and drug containing Xanthan Gum tablets are listed in Figures 5.10. to 5.12. and Figures 5.13. to 5.15. respectively. For blank and Orphenadrine Citrate containing tablets a steady swelling process was the most apparent feature noted. This was preceded by a short erosive period in Orphenadrine Citrate containing tablets, which also underwent a slower swelling process in comparison to blank tablets. For Orphenadrine HCl containing tablets (Figures 5.12. and 5.15.) the previously noted lengthy erosive process was apparent, and it was proceeded with a gradual retrieval of the swelling ability of the tablets. Crack formation was observed on the radial faces of Orphenadrine HCl containing tablets. However, and in a manner similar to that observed with round tablets, the nature of such cracks was less profound than that noted on the sides of the tablets.

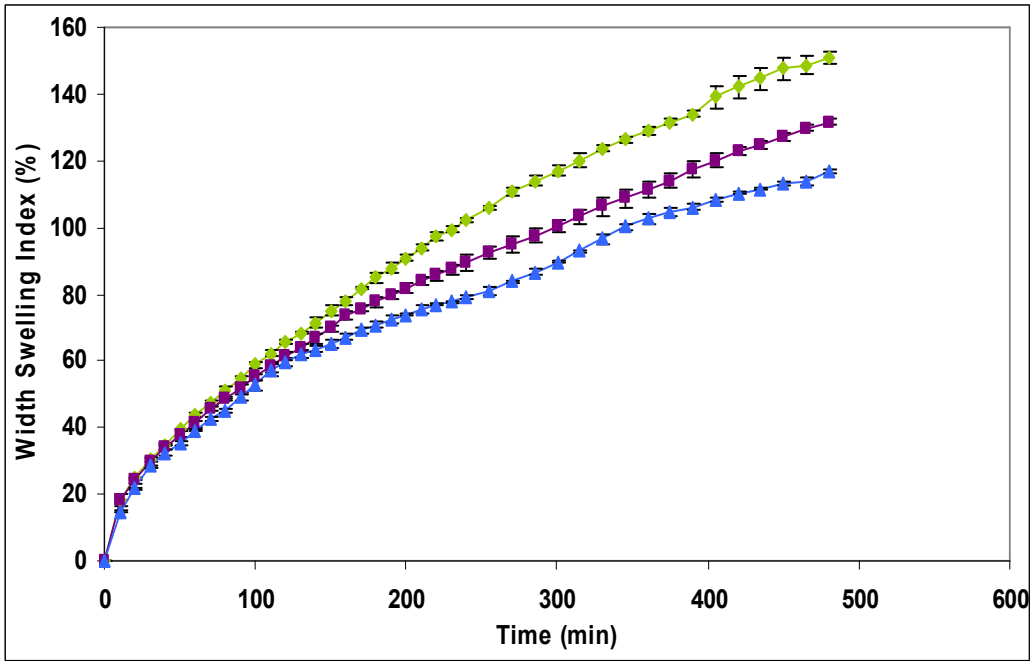

Figure 5.10. Width swelling profiles of elongated blank Xanthan Gum tablets, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

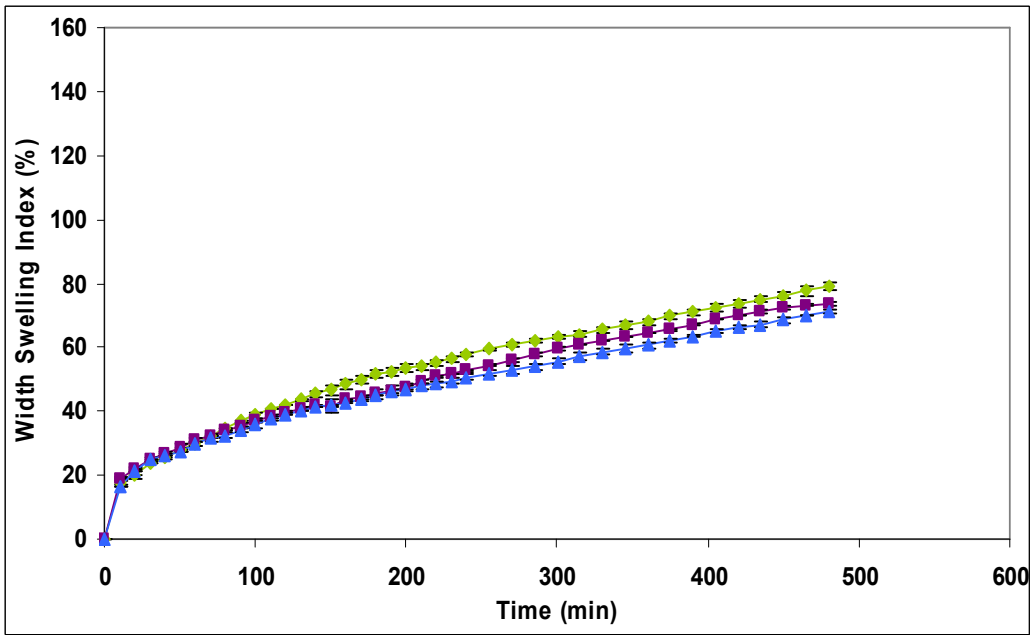

Figure 5.11. Width swelling profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

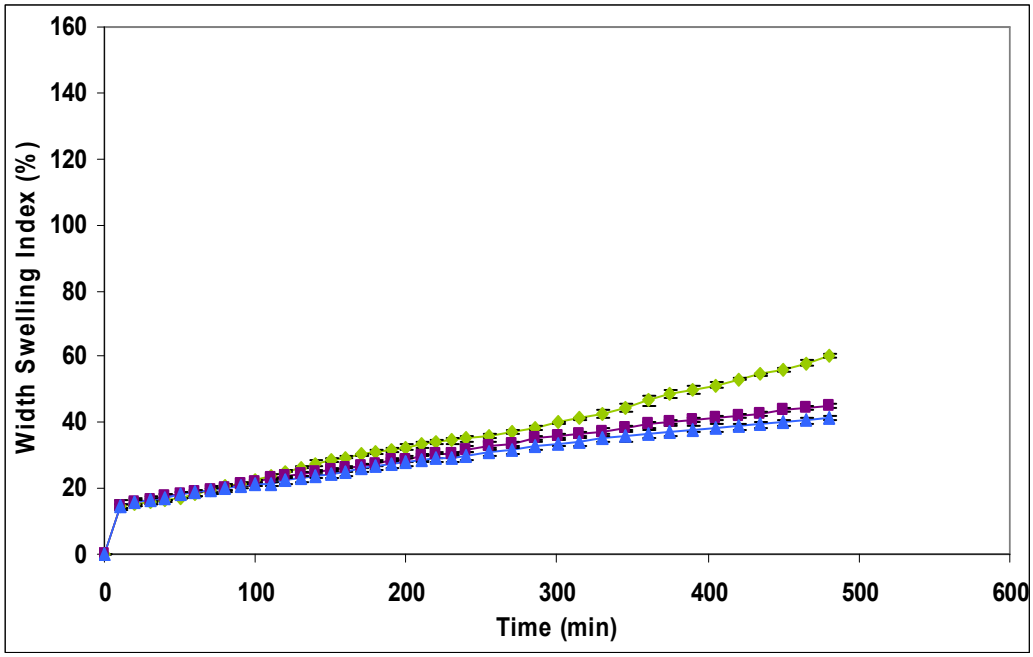

Figure 5.12. Width swelling profiles of elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

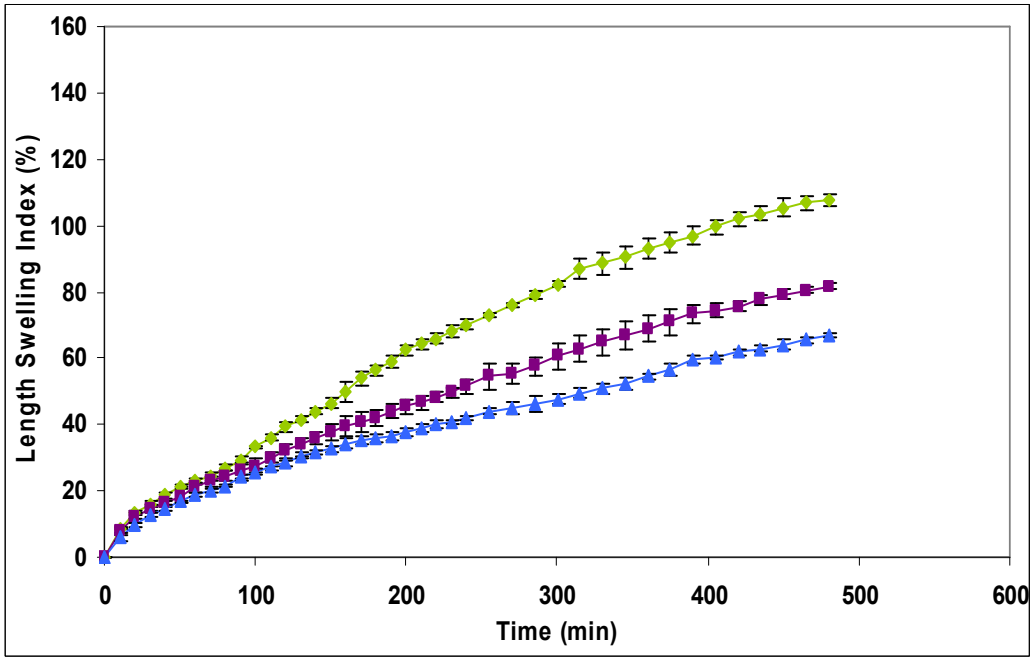

Figure 5.13. Length swelling profiles of elongated blank Xanthan Gum tablets, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

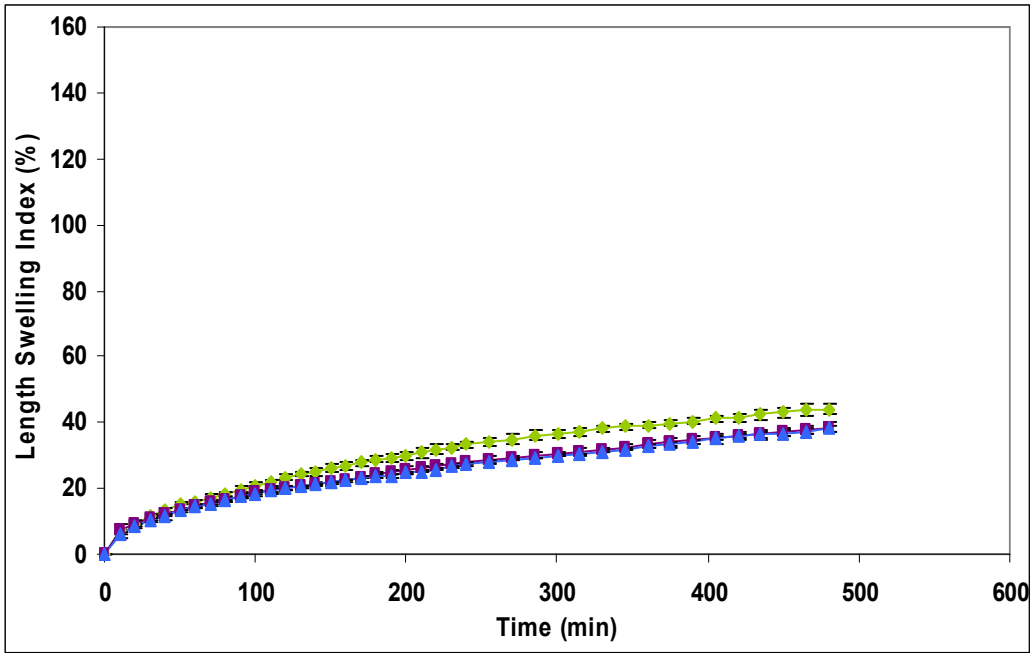

Figure 5.14. Length swelling profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

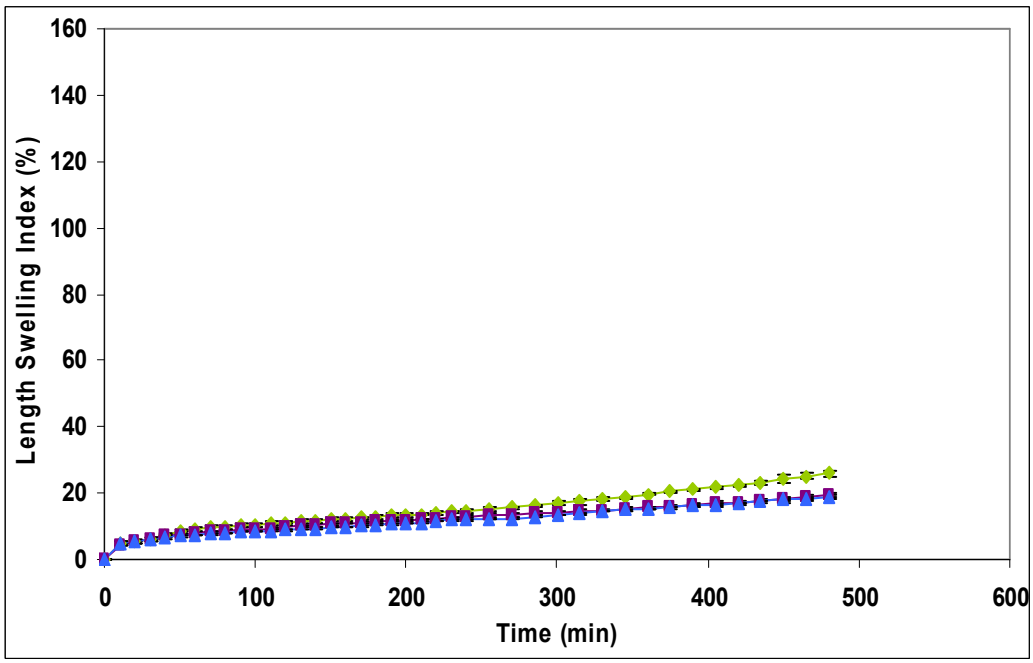

Figure 5.15. Length swelling profiles of elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%. -♦-(curvature 0 mm), -■-(curvature 1 mm), -▲-(curvature 2 mm), (n=3).

5.3.2.4. Statistical comparison of the width swelling profiles of elongated tablets:

The results of the two-way ANOVA investigations conducted on the width swelling profiles of blank and drug containing elongated Xanthan Gum tablets are presented in Tables 5.12. to 5.14., respectively. For blank tablets (Table 5.12.) a significant influence on the width swelling of the elongated tablets was noted with both studied factors, i.e. tablet face curvature degree and overall porosity. Moreover, a significant interaction was noted between both factors

In order to further clarify such significant interaction observed between the two main factors, multiple one-way ANOVAs were conducted for each degree of tablet overall porosity separately to examine the effect associated with tablet face curvature degree. Furthermore, every investigation was followed by post hoc analysis using the Sheffé test. It was noted that the width swelling indices of flat tablets were significantly higher than those of tablets with the two higher degrees of face curvature which were statistically similar. A similar pattern was observed with tablets produced at all three overall porosity values, with only small differences between tablets having different porosities. A similar result was obtained with the two-way ANOVA investigation at 240 minutes. However, the results of the Sheffé test indicated the presence of significant differences between all three levels of tablet face curvature; flat tablets had the highest swelling indices, and the decrease in the

values was statistically significant with the increase in tablet face curvature ratio.

At 480 minutes, only the two main factors had a significant influence on tablet width swelling. No significant interaction was noted between the factors, and thus the influence of each factor has to be interpreted seperately. The results of the Sheffé test indicated a pattern similar to that observed at 240 minutes with regards to the influence of tablet face curvature, i.e. significant difference between all three values of face curvature. As for tablet porosity the only significant difference was observed between tablets with an overall porosity of 15% and those with an overall porosity of 20%, and even between those two types of tablets, the difference in the values of width swelling indices were very small.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	5.819	0.011
	Curvature	2	151.055	< 0.001
	Porosity*Curvature	4	10.789	< 0.001
240	Porosity	2	12.534	< 0.001
	Curvature	2	485.572	< 0.001
	Porosity*Curvature	4	5.142	0.006
480	Porosity	2	5.973	0.010
	Curvature	2	1158.775	< 0.001
	Porosity*Curvature	4	1.800	0.173

Table 5.12. Two -way ANOVA results for the width swelling of elongated blank Xanthan Gum tablets.

Two-way ANOVA investigation of the width swelling profiles of Orphenadrine Citrate containing tablets (Table 5.13.) indicated a uniform pattern at all three time points investigated in which the only factor to exert a significant influence on the width swelling of the elongated tablets is actually the degree of tablet face curvature, as indicated by the p values associated with this factor. No significant influence was associated with tablet overall porosity, and no significant interaction was observed between the two main factors, i.e. the degree of tablet face curvature and tablet overall porosity. The results of the Sheffé test indicated a statistically significant difference between all three degrees of tablet face curvature, with the values associated with flat tablets being highest. The same pattern of behaviour was noted at all three time points.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.864	0.438
	Curvature	2	73.554	< 0.001
	Porosity*Curvature	4	0.671	0.620
240	Porosity	2	1.639	0.222
	Curvature	2	129.849	< 0.001
	Porosity*Curvature	4	0.694	0.606
480	Porosity	2	0.916	0.418
	Curvature	2	214.254	< 0.001
	Porosity*Curvature	4	0.678	0.616

Table 5.13. Two -way ANOVA results for the width swelling of elongated Xanthan Gum tablets with Orphenadrine Citrate.

A similar pattern was observed with elongated tablets containing the drug Orphenadrine HCl (Table 5.14.) with the degree of tablet face curvature

being the only factor to exert a significant influence on the width swelling of tablets, and a significant difference being present between all three levels of tablet face curvature

Swelling time (min)	Variable	df	F	p
120	Porosity	2	0.117	0.890
	Curvature	2	25.464	< 0.001
	Porosity*Curvature	4	0.456	0.767
240	Porosity	2	1.865	0.184
	Curvature	2	39.410	< 0.001
	Porosity*Curvature	4	0.352	0.839
480	Porosity	2	0.955	0.403
	Curvature	2	511.604	< 0.001
	Porosity*Curvature	4	0.300	0.874

Table 5.14. Two -way ANOVA results for the width swelling of elongated Xanthan Gum tablets with Orphenadrine HCl.

5.3.2.5. Statistical comparison of the length swelling profiles of elongated tablets:

The results of the two-way ANOVA investigations conducted on the length swelling indices of blank and drug containing elongated Xanthan Gum tablets are listed in Tables 5.15. to 5.17., respectively. For blank Xanthan Gum tablets (Table 5.15.), initially at 120 minutes, both studied factors, i.e. degree of tablet face curvature and tablet overall porosity had a significant influence on tablet length swelling indices. Moreover, the interaction between the two factors was significant. With further hydration at 240 minutes only the degree of tablet face curvature had a significant

influence on tablet length swelling, but a significant interaction was noted between this factor and the overall porosity of the tablets. At 480 minutes the influence of the degree of tablet face curvature on tablet length swelling continued to be significant. However, no significance was associated with tablet overall porosity or the interaction between both of the previous factors.

After conducting one-way ANOVA to investigate the influence of tablet face curvature at each level of tablet overall porosity and performing post hoc analysis using the Sheffé test. A pattern similar to that observed with tablet width swelling indices was noted, where initially at 120 minutes the swelling indices of flat tablets where significantly higher than those associated with tablets with the two higher degrees of face curvature which were statistically similar. With further hydration at 240 minutes and 480 minutes a significant difference was noted between the swelling indices of tablets with all three degrees of tablet face curvature with those associated with flat tablets being highest.

For tablets containing both drugs (Tables 5.16. and 5.17.) a significant influence on tablet length swelling was only noted with the degree of tablet face curvature at all three time points investigated. The results of the Sheffé test conducted for the significant factor; i.e. tablet face curvature degree, indicated that for elongated tablets containing the drug Orphenadrine Citrate, at all three time points, the length swelling indices of flat tablets were significantly higher than those of tablets with higher degrees of face curvature. However, no statistically significant differences

were observed between the two higher degrees of tablet face curvature, i.e. 1 mm and 2 mm. Such patterns could be explained in terms of the higher hydration potential associated with flat tablets due to their lower volume.

As for tablets containing the drug Orphenadrine HCl, initially at 120 minutes and 240 minutes significant differences were observed between the length swelling indices of tablets produced at all three levels of tablet face curvature, with those associated with flat tablets being highest. With further hydration at 480 minutes the only significant difference was noted between the length swelling indices of flat tablets and those of tablets with higher degrees of face curvature. However, no significant difference was noted between the two higher degrees of face curvature of 1 and 2 mm.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	14.848	< 0.001
	Curvature	2	305.048	< 0.001
	Porosity*Curvature	4	14.390	< 0.001
240	Porosity	2	3.417	0.055
	Curvature	2	1480.830	< 0.001
	Porosity*Curvature	4	5.961	0.003
480	Porosity	2	0.711	0.504
	Curvature	2	2154.859	< 0.001
	Porosity*Curvature	4	0.709	0.596

Table 5.15. Two -way ANOVA results for the length swelling of elongated blank Xanthan Gum tablets.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	2.061	0.156
	Curvature	2	96.852	< 0.001
	Porosity*Curvature	4	0.893	0.488
240	Porosity	2	0.072	0.931
	Curvature	2	179.731	< 0.001
	Porosity*Curvature	4	1.311	0.304
480	Porosity	2	0.851	0.444
	Curvature	2	88.093	< 0.001
	Porosity*Curvature	4	0.265	0.897

Table 5.16. Two -way ANOVA results for the length swelling of elongated Xanthan Gum tablets with Orphenadrine Citrate.

Swelling time (min)	Variable	df	F	p
120	Porosity	2	2.418	0.117
	Curvature	2	137.858	< 0.001
	Porosity*Curvature	4	0.856	0.509
240	Porosity	2	1.654	0.219
	Curvature	2	153.082	< 0.001
	Porosity*Curvature	4	1.748	0.183
480	Porosity	2	0.025	0.975
	Curvature	2	242.951	< 0.001
	Porosity*Curvature	4	0.266	0.896

Table 5.27. Two -way ANOVA results for the length swelling of elongated Xanthan Gum tablets with Orphenadrine HCl.

In a manner similar to that observed with round tablets, and upon comparing the differences between the various swelling profiles associated with blank and drug containing elongated Xanthan Gum tablets, it becomes clear that the differences in the swelling ability of

tablets produced with the different degrees of face curvature is more profound within blank tablets in comparison to drug containing tablets. This can also be noted by looking at the higher values of the F ratios associated with the factor of tablet face curvature degree in blank elongated tablets in comparison to drug containing ones.

5.3.3. Microscopic examination of hydrated tablets:

The results of the swelling studies of both round and elongated tablets indicated a clear difference in the swelling ability of tablets produced using the three different formulations used in this study. Most noticeable was the lower swelling ability of tablets containing either of the two model drugs in comparison with the blank tablets. This was particularly noticeable in tablets containing the drug Orphenadrine HCl in which a highly irregular gel layer was formed in the initial phase of tablet hydration. The formation of the gel layer due to polymer swelling is considered the main factor contributing to the overall expansion of hydrophilic matrix tablets during the span of the hydration process. It was thus necessary to get further insight into the structural properties of the gel layer formed on the surface of tablets produced using all three formulations. This was accomplished by microscopic imaging of the gel layer formed on the hydrated surface of the different tablets.

Dosage form variables in terms of shape, curvature and porosity were kept constant during this part of the work to eliminate any differences cause by them; round tablets with a face Curvature ratio of 0 and overall

tablet porosity of 15% were used in this part to focus on the differences caused by the change in the formulation used.

The gel layer formed on the radial face of blank and drug containing Xanthan Gum tablets are shown in Figures 5.16. to 5.18., respectively. The gel layer formed on the radial face of blank Xanthan Gum tablets (Figure 5.16.) appears to be porous in general. However, the size and shape distribution of the pores apparent on the surface is clearly wide; pores of various sizes and shapes are clearly seen.

The gel layer formed on the radial surface of tablets containing the drug Orphenadrine Citrate (Figure 5.17.) appears to be denser in comparison to the other tablets, indicating a change in the hydration properties of the system. However, pores of varying sizes and shapes are also visible on the surface of the gel layer.

Examination of the gel layer formed on the radial surface of tablets containing the drug Orphenadrine HCl during the initial phase of tablet hydration (Figure 5.18.) revealed a structure that is more porous in comparison to the other tablets. A greater number of large pores are seen in the structure of the gel layer.

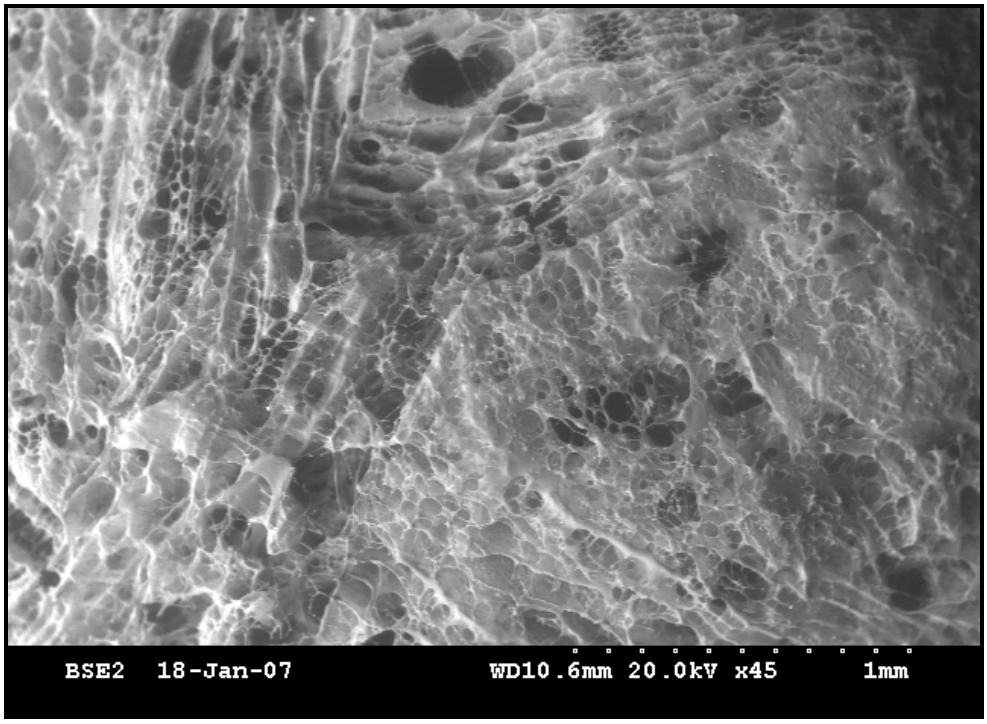

Figure 5.16. SEM image of the surface of a hydrated round blank Xanthan Gum tablet (R/D = 0, porosity 15%, magn. 45X).

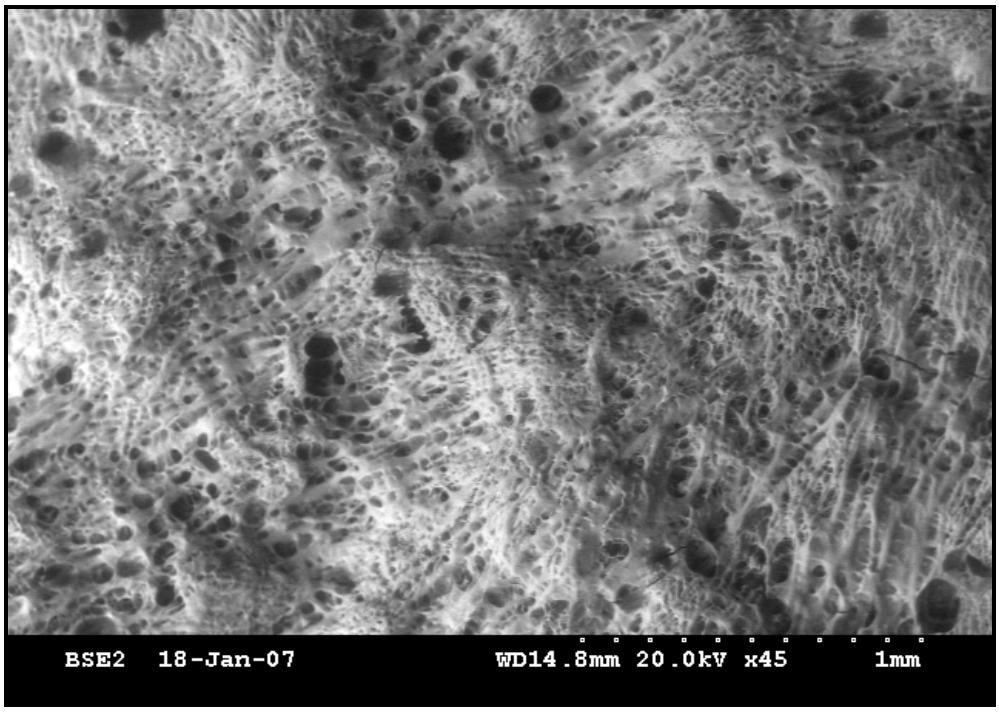

Figure 5.17. SEM image of the surface of a hydrated round Xanthan Gum tablet with Orphenadrine Citrate (R/D = 0, Porosity 15%, magn. 45X).

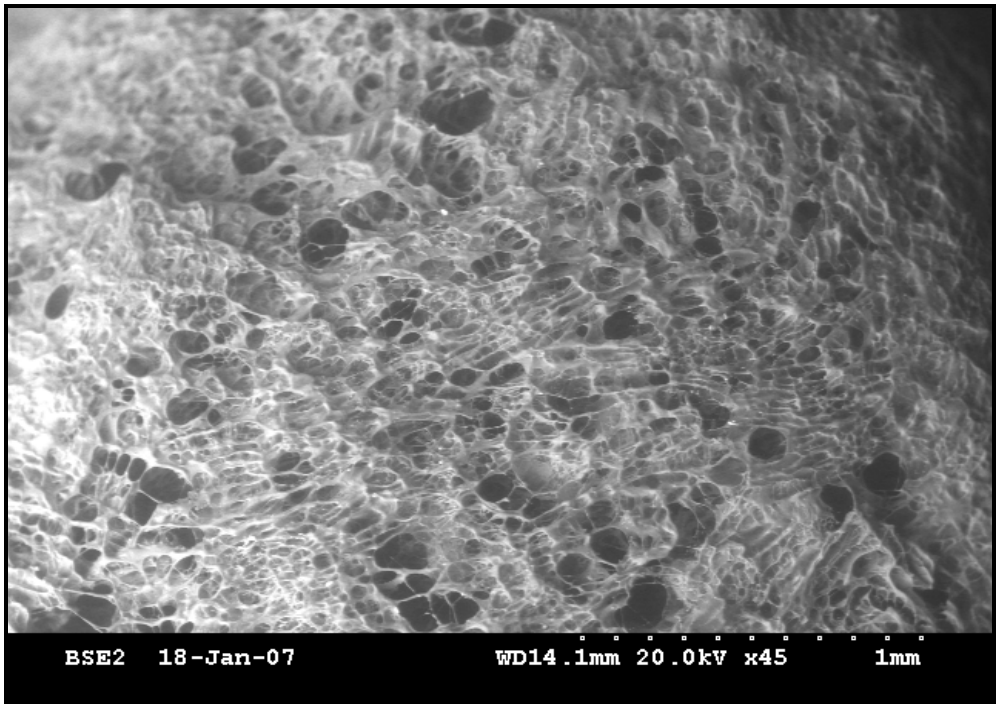

Figure 5.18. SEM image of the surface of a hydrated round Xanthan Gum tablet with Orphenadrine HCl (R/D = 0, porosity 15%, magn. 45X).

5.4 General discussion and conclusions:

The results of this chapter indicated that changing the shape parameters of Xanthan Gum hydrophilic matrix tablets had a mixed effect on the swelling and expansion ability of both round and elongated tablets. The influence of changing the degree of tablet face curvature on tablet swelling ability was much more profound than that associated with the change in tablet overall porosity within the range of porosities investigated in this study.

Another important observation was that the nature of the effect associated with tablet face curvature varied between tablets produced using the three different formulations investigated in this study. Moreover,

the influence associated with tablet overall porosity clearly changed in terms of both; its significance, and its potential interaction with the influence associated with the degree of tablet face curvature, with the change of the formulation used in tablet production.

Such observations indicated that the process of tablet swelling and expansion was dually governed by the nature of formulation used in tablet production and the degree of face curvature of the produced tablets, with minimal influence exerted by tablet overall porosity.

CHAPTER SIX

6. Characterisation of Xanthan Gum gel systems:

6.1. Introduction:

The results of tablet hydration studies indicated a clear influence of the type of formulation used in tablet production on the hydration and swelling patterns of the produced tablets. Moreover, the nature of the hydration behaviour, especially for tablets containing the drug Orphenadrine HCl, appeared to be time dependent, with multiple stages observed in the hydration process of such tablets. Thus it was crucial to further investigate the hydration patterns associated with the various tablets, and furthermore, to characterise the properties associated with the gel layer formed within such tablets.

The overall aim of this part of the work was to give further insight into the nature of the gel layer formed within the hydrating matrix tablets used in this study, by means of rheological and thermal studies.

Rheological studies, which enable the investigation of the structural and flow properties of gel systems, were used to characterise the properties

of Xanthan Gum hydrated gel systems. Gels which mimic in their concentration and content the outer region in the gel layer of a hydrating hydrophilic matrix tablet were used. Two main types of rheological studies were employed in this investigation. Initially, oscillation studies were used. During these studies the gel samples were subjected to small sinusoidal oscillating stresses without destroying the gel structure, in order to determine the viscous “liquid” and elastic “solid” properties of the gels. The second step comprised the use of viscometric studies in which the gel structure was destroyed by applying larger rotational stresses. This allowed the determination of the flow properties of the gel systems.

Thermal investigations were carried out using modulated differential scanning calorimetry which provided some insight into the physico-chemical properties of the gel layer formed on the surface of the studied tablets.

6.2. Results and discussion:

6.2.1. Rheological studies:

Clear differences were visually observed in the properties of gels prepared using the different formulations used in this study. Gels prepared using the blank Xanthan Gum formulation, and gels prepared using the formulations containing the drug Orphenadrine Citrate, were highly viscous. Moreover, the apparent viscosity of these gels increased with increased gel concentration. However, gels prepared using the

formulation containing the drug Orphenadrine HCl exhibited a rather different behaviour; at a concentration of 2% w/w, such gels had a consistency similar to that with blank and Orphenadrine Citrate containing gels prepared at the same concentration. Upon increase in gel concentration, a marked drop in gel structure was clearly visible; gels containing Orphenadrine HCl prepared at a concentration of 4% w/w had the consistency of a weak slurry system. Further increase in gel concentration to 6% w/w resulted in a much more significant drop in gel structure resulting in highly sedimenting particulate suspensions. Moreover, no gel formation or increase in viscosity was observed with time, even after continuous stirring for 30 minutes and storage for 24 hours. These gel systems, i.e. systems prepared at a concentration of 6% w/w using the formulation containing the drug orphenadrine HCl, did not give consistent rheological measurements. This may be due to their high sedimentation rate which resulted in the occurrence of artefacts in the results. Thus no rheological measurements are reported for these.

6.2.1.1. Oscillation studies:

Initially, strain amplitude sweeps were carried out on all gel systems to determine the linear viscoelastic region (LVR) for each gel sample. Within this region the shear strain or deformation within a material is directly proportional to the applied shear stress. The relationship between the shear stress and shear strain was monitored using two parameters, the elastic modulus (G') and the viscous modulus (G"). These parameters are the two components of the overall complex modulus (G*) which is the

mathematical parameter describing the relationship obtained by dividing the shear stress by the corresponding shear strain (Barnes et al 1996). The elastic, or storage, modulus (G') reflects the part of the shear stress which is said to be in phase with the shear strain under sinusoidal conditions divided by the corresponding strain (Barnes et al 1996). This parameter is associated with the solid nature of the material. The viscous, or loss, modulus (G") is an imaginary part of the complex modulus (Barnes et al 1996). This parameter in turn is associated with the liquid nature of the material.

The results of the amplitude sweeps for the various gel systems investigated are shown in Figures 6.1. to 6.4. For blank Xanthan Gum gels, and gels containing the drug Orphenadrine Citrate, rather broad linear viscoelastic regions were detected for gels prepared at the three concentrations studied, covering most of the strain amplitude range studied. Moreover, the values of the elastic modulus (G') for these gels are consistently higher than the values for the viscous or loss modulus (G"), indicating the presence of a rather solid structure. Such behaviour could be attributed to the ability of these systems to form a stable and consistent three dimensional gel network. Deflection points in the curves representing both the elastic (G') and viscous (G") moduli, are only apparent at higher amplitude values indicating the loss of gel structure at high amplitudes. Upon comparison between the values of elastic (G') and viscous (G") moduli for gels prepared using the same formulation but at different concentrations, a clear increase is observed in the values of both

moduli upon increase in gel concentration. The increase in moduli values is more apparent upon increase in gel concentration from 2% w/w to 4% w/w, with smaller increase upon further increase in gel concentration to 6% w/w. Such behaviour became more apparent in gel systems containing the drug Orphenadrine Citrate.

As for gel systems containing the drug Orphenadrine HCl, and as previously mentioned, a rather opposite behaviour was apparent in the results of the amplitude sweeps; gels prepared at a concentration of 2% w/w exhibited a broad linear viscoelastic region (LVR), in which the values of the elastic modulus (G') are consistently higher than those of the viscous modulus (G"). This is comparable to the results obtained for gels prepared at the same concentration using the two other formulations.

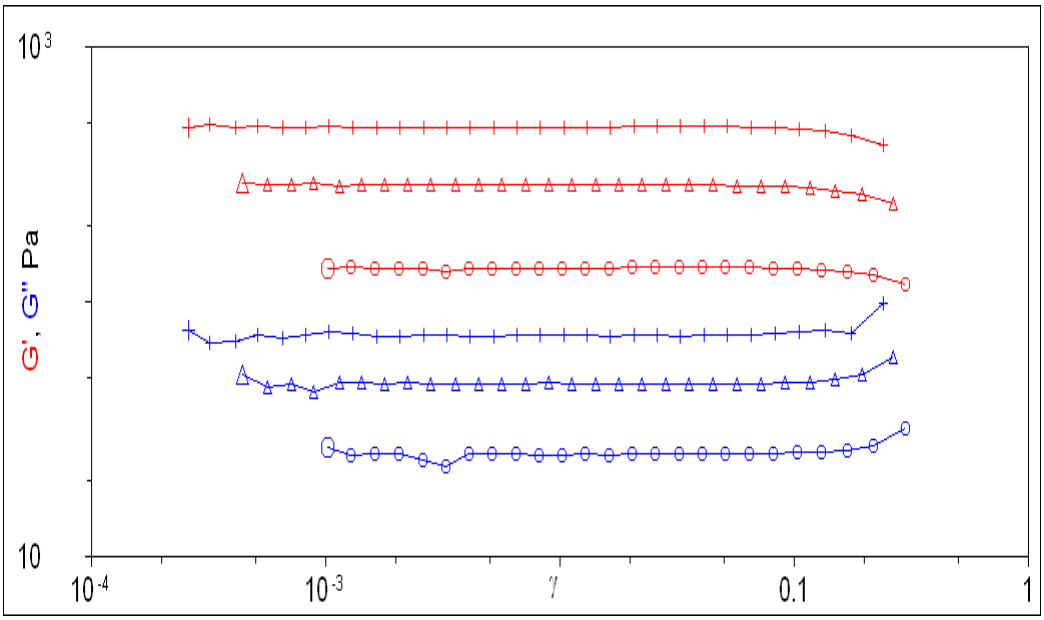

Figure 6.1. Amplitude sweep of blank Xanthan Gum gels. Red signs indicate the elastic modulus (**G'**), and blue signs indicate the viscous modulus (**G"**). (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

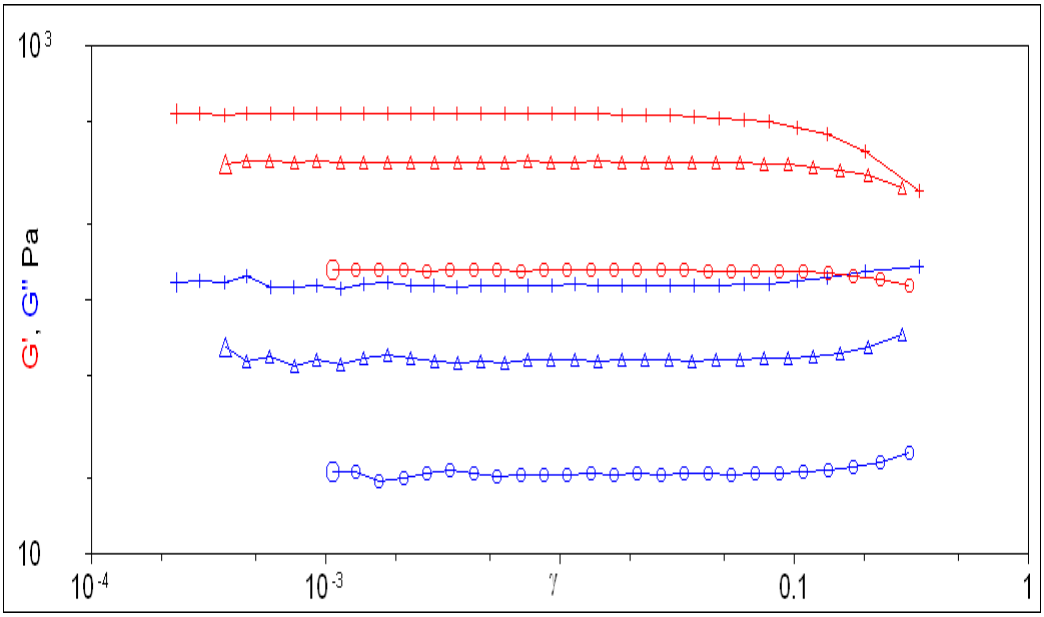

Figure 6.2. Amplitude sweep of Xanthan Gum gels with Orphenadrine Citrate. Red signs indicate the elastic modulus (**G'**), and blue signs indicate the viscous modulus (**G"**). (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

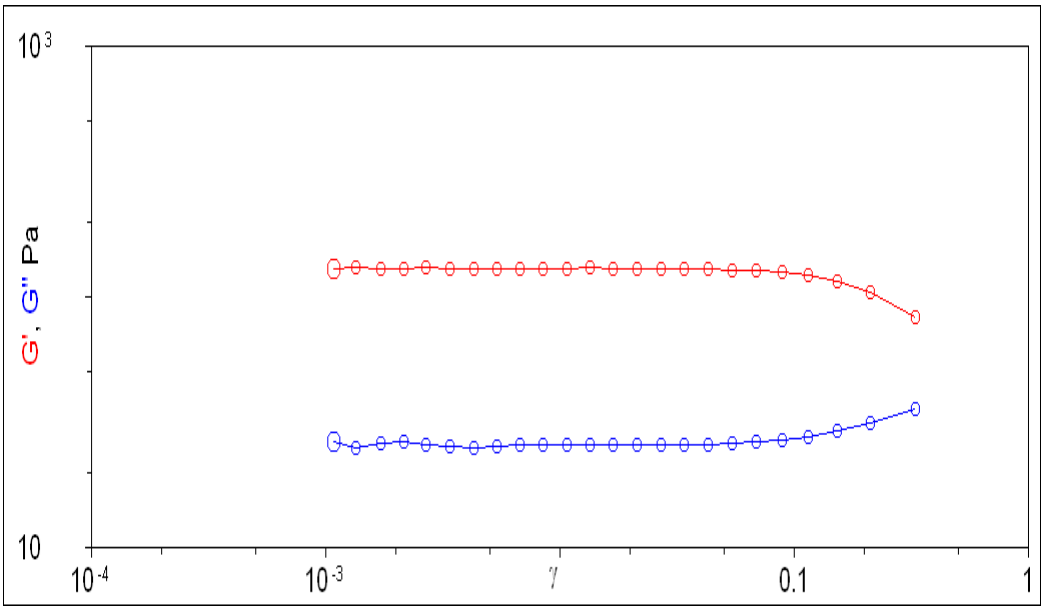

Figure 6.3. Amplitude sweep of 2% w/w Xanthan Gum gel with Orphenadrine HCl. Red signs indicate the elastic modulus (**G'**), and blue signs indicate the viscous modulus (**G"**).

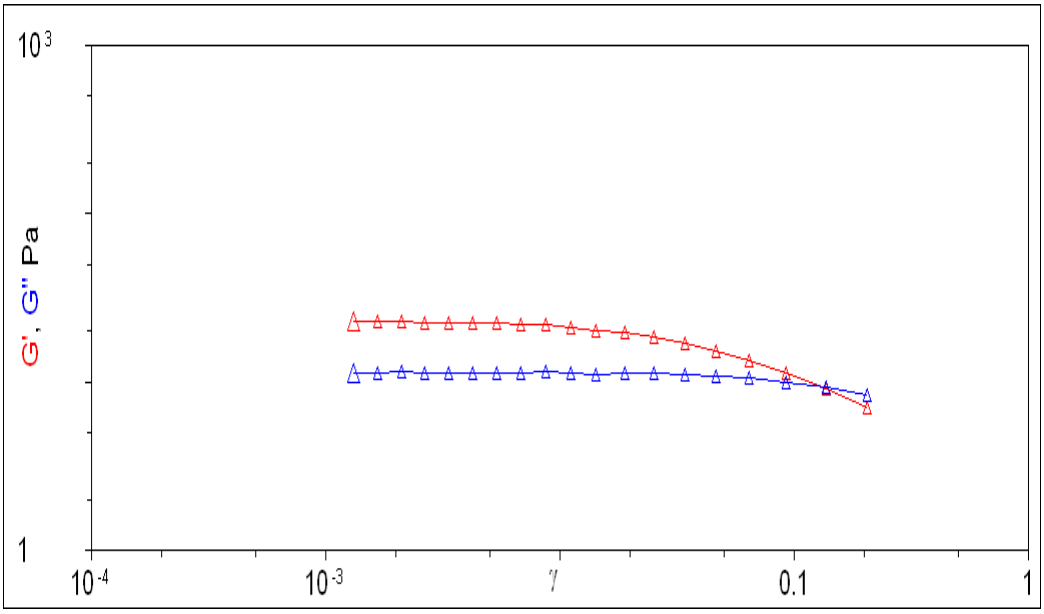

Figure 6.4. Amplitude sweep of 4% w/w Xanthan Gum gel with Orphenadrine HCl. Red signs indicate the elastic modulus (**G'**), and blue signs indicate the viscous modulus (**G"**).

However, upon increase in the concentration of the gel system a sharp drop in the values of both elastic (G') and viscous (G") moduli was apparent and a much smaller linear viscoelastic region was obtained. This is consistent with the visual observation of this gel system which had the consistency of pourable slurry. Within the linear viscoleastic region the values of the elastic modulus (G') are consistently higher than those of the viscous modulus (G") but the magnitude of the difference between these values is much smaller than for the other gel systems investigated. Moreover, the breakdown in gel structure occurred at lower values of amplitude.

Strain amplitude values obtained from the middle point of the linear viscoelastic region (LVR) for each of the gel systems investigated.

Together with the corresponding stress values, these values were used to obtain a dynamic spectrum for the rheological behaviour of the various gel systems across a frequency range between 0.01 and 10 Hz. For all gels a strain value of 0.01 was used in the frequency sweep investigation. One exception was the 4% w/w gel system containing the drug Orphenadrine HCl, where a strain value of 0.005 was used due to the previously mentioned nature of the linear viscoelastic region associated with such samples.

The influence of oscillation frequency on the values of both, elastic (G') and viscous (G") moduli for the various gel systems investigated in this study are shown in Figures 6.5. to 6.7. Once again, certain trends are apparent in the behaviour of the various gel systems. For blank Xanthan Gum gels the results of the frequency sweeps show values of the elastic modulus (G') that are consistently higher than those for the viscous modulus (G"). The difference between the values of both moduli is clearly apparent, and is within the range of one order of magnitude. No crossover point is detected within the frequency range investigated, and this is apparent for gels prepared at all concentrations. Moreover, the values of both moduli seem to have a certain degree of frequency dependence, with higher values obtained at higher values of oscillation frequency. This behaviour of frequency dependence is more apparent in the values of the elastic modulus (G'). Such behaviour is in agreement with previously published work that investigated the dynamic rheological behaviour of Xanthan Gum gels prepared at such higher concentrations;

Talukdar et al (1996) characterised Xanthan Gum gels prepared at concentrations of 4% and 7% w/w, and they reported similar finding where the values of the elastic modulus (G') were consistently higher than those of the viscous modulus (G") across a wide range of oscillation frequencies. This behaviour associated with Xanthan Gum was previously associated with the ability of this polysaccharide to form weak three dimensional gel structures. This was apparent at moderate gel concentration of 0.5%, 1% and higher. However, loss of this behaviour was apparent at lower concentration values (Lim et al 1984, Rochefort and Middleman 1987).

Inclusion of the two drugs into the Xanthan Gum gel systems seems to have a different effect on the dynamic rheological properties of such systems. Gels containing the drug Orphenadrine Citrate exhibit a dynamic behaviour similar to that obtained with blank Xanthan Gum gel systems, in which the values of the elastic modulus (G') are consistently higher that those of the viscous modulus (G") throughout the frequency range investigated with slight frequency dependence observed in the values of both moduli; higher values were apparent at higher fruequency especially for the values of the elastic modulus (G'). No crossover point was apparent with the gels prepared at any of the concentrations investigated, and the values of both moduli progressively increased with increased gel concentration. Such systems could be defined with respect to previously published criteria as having weak-gel structures, where the elastic modulus (G') is much larger than the viscous modulus (G"). Slight

frequency dependence is observed in the values of the moduli (Ross Murphy and Shatwell 1993).

Inclusion of the drug Orphenadrine HCl had a different effect. This was mainly apparent in the effect associated with the increase in gel concentration. Gels with a concentration of 2% w/w exhibited a behaviour similar to that observed with blank and Orpheadrine Citrate containing 2% w/w gels; a slight frequency dependence was observed, and the values of elastic Modulus (G') were consistently higher than those of the viscous modulus (G"). Furthermore, no crossover point was detected within the investigated frequency range.

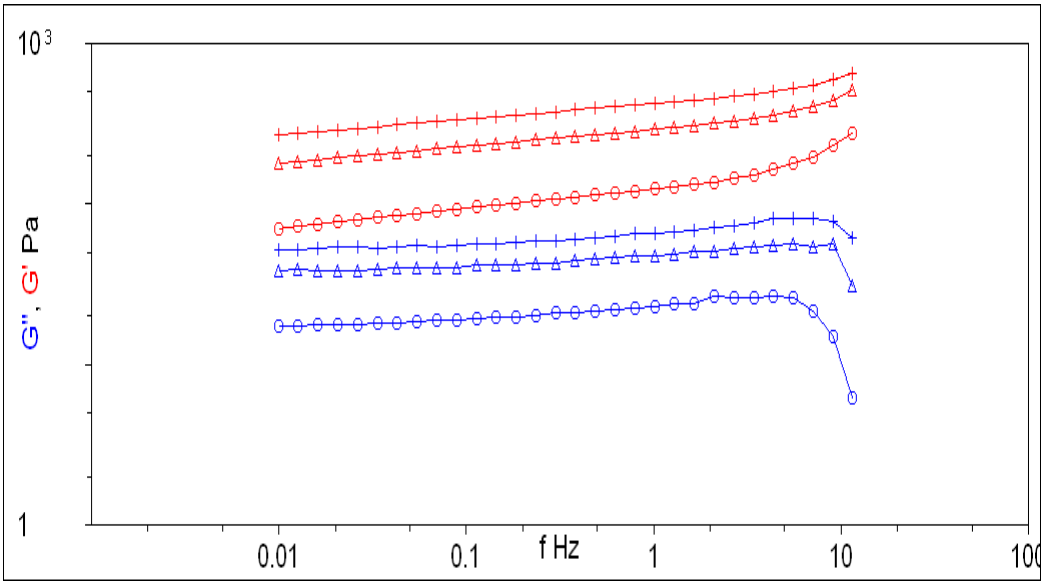

Figure 6.5. Influence of frequency on the elastic modulus (**G'**), and Viscous modulus (**G"**) of blank Xanthan Gum gels. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

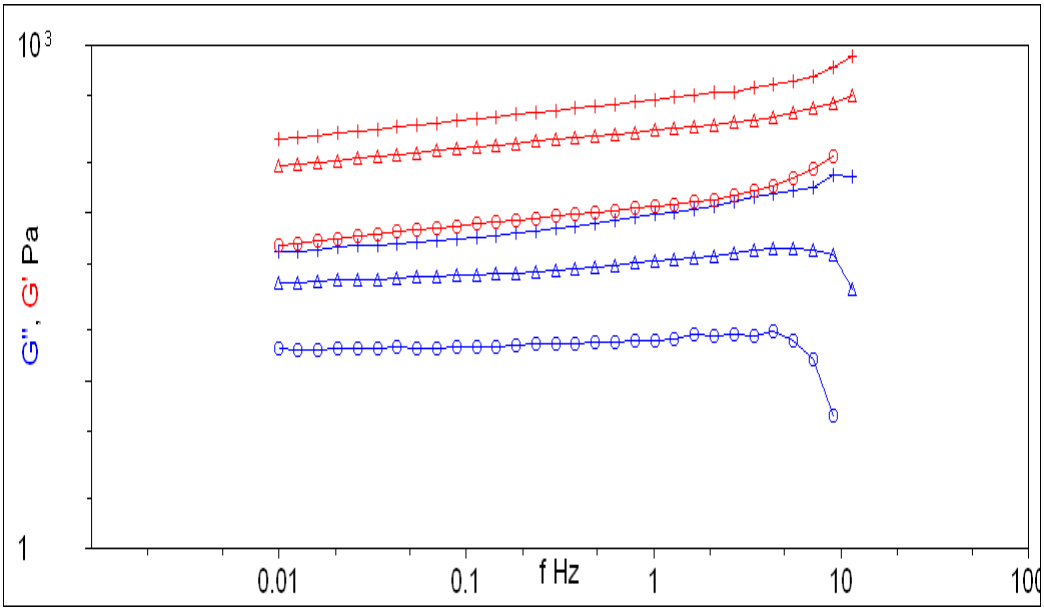

Figure 6.6. Influence of frequency on the elastic modulus (**G'**), and Viscous modulus (**G"**) of Xanthan Gum gels with Orphenadrine Citrate. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

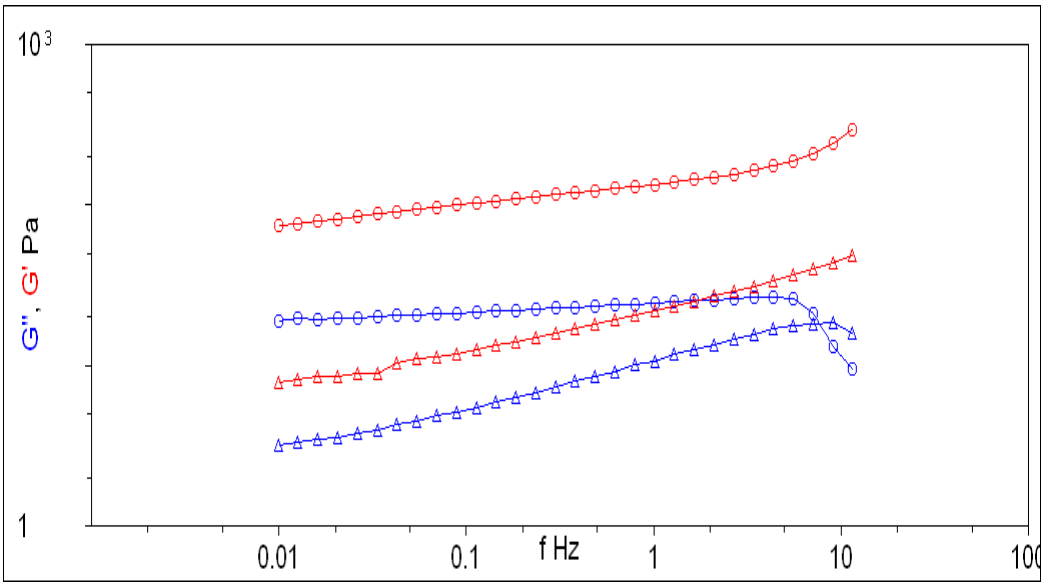

Figure 6.7. Influence of frequency on the elastic modulus (**G'**), and Viscous modulus (**G"**) of Xanthan Gum gels with Orphenadrine HCl. (O) 2% w/w gel, (Δ) 4% w/w gel.

On the other hand, gels with a concentration of 4% w/w exhibited much lower values for both the elastic (G'), and viscous (G") moduli. The frequency dependence of the moduli values for these gels were much more apparent than those of all other gel systems investigated; values were clearly higher at higher frequencies. However, within the range of oscillation frequencies investigated, no crossover point was apparent, especially at the lower frequency values, which is usually associated with the phase transition between polymer gel and polymer solution. Such behaviour indicates that even at such consistency, a three dimensional gel structure was still apparent in the system.

More insight into the structural features associated with the various gel systems investigated could be attained by observing the effect of oscillation frequency on the phase angle, or phase lag, values associated with the gel systems. These values represent the phase difference, or lag, between the stress and strain waves within a material during sinusoidal oscillation. A material with a pure elastic "solid" behaviour would produce a phase lag of 0°, whereas a material with a pure viscous "liquid" behaviour would produce a phase lag of 90° (Marriott 2002).

The effect of oscillation frequency on the phase angle of the various gel systems studied is presented in Figures 6.8. to 6.10. For blank Xanthan Gum gels (Figure 6.8), slightly higher phase angle values were observed at lower oscillation frequency values. This was apparent with gel systems prepared at all three concentrations of 2%, 4% and 6% w/w. Moreover,

the values of the phase angle seem to undergo a slight decrease with the increase in gel concentration. However, changes in the values of phase angle observed in these gel systems and the change in such values with frequency and concentration seem to be minimal with phase angle values ranging between about 9.0° and 13.0° for all samples. Thus, all blank Xanthan Gum gels investigated could be considered as having a solid gel structure due to the low phase angle values associated with these systems. A somewhat similar observation was apparent with gel systems containing the drug Orphenadrine Citrate (Figure 6.9), where similar variations in phase angle values where observed with changes in oscillation frequency and gel concentration. One irregular observation was noted with 6% w/w gel systems containing Orphenadrine Citrate in which phase angle values were slightly higher than those obtained with gels prepared at concentrations of 2% w/w and 4% w/w, which usually indicates a more liquid like structure. However, the differences between phase angle values at different oscillation frequencies and gel concentrations were once again minimal and ranged between 9.0° and 13.5°.

Gels prepared at a concentration of 2% w/w and containing the drug Orphenadrine HCl (Figure 6.10), had slightly higher phase angle values when compared to blank and Orphenadrine Citrate containing gels with similar concentration. They exhibited phase angle values ranging between 11.5 ° to 15.3° across the frequency range investigated.

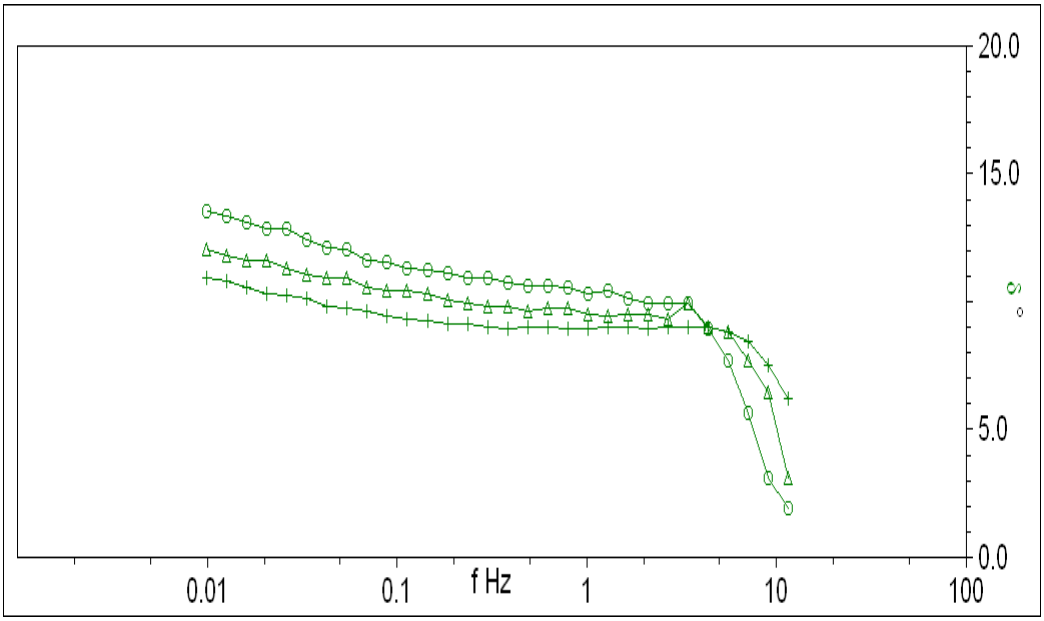

Figure 6.8. Influence of frequency on the phase angle (**δ**) of blank Xanthan Gum gels. (**O**) 2% w/w gel, (Δ) 4% w/w gel, and (**+**) 6% gel.

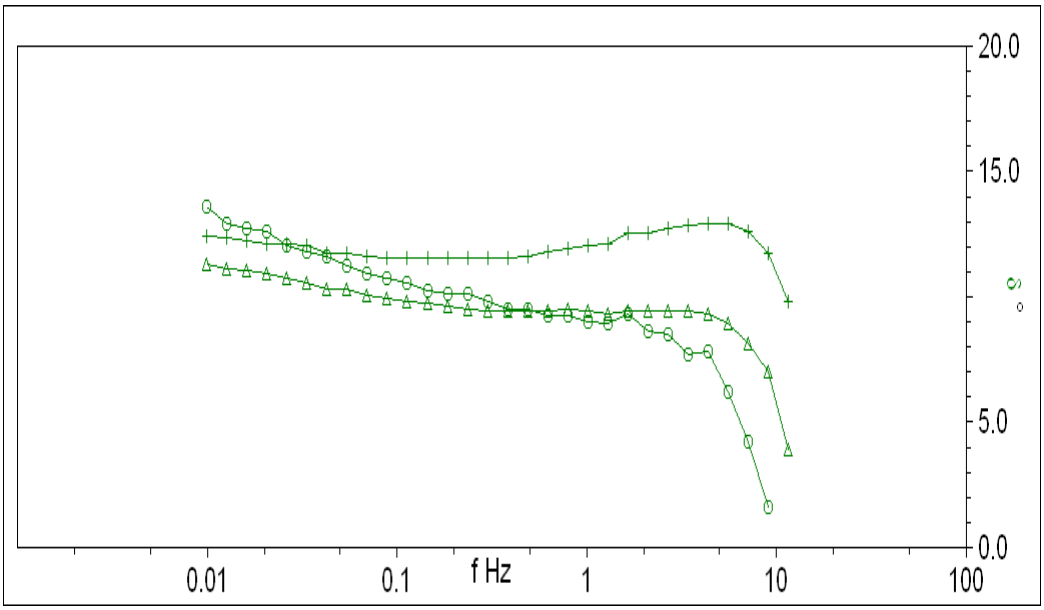

Figure 6.9. Influence of frequency on the phase angle (**δ**) of Xanthan Gum gels with Orphenadrine Citrate. (**O**) 2% w/w gel, (Δ) 4% w/w gel, and (**+**) 6% gel.

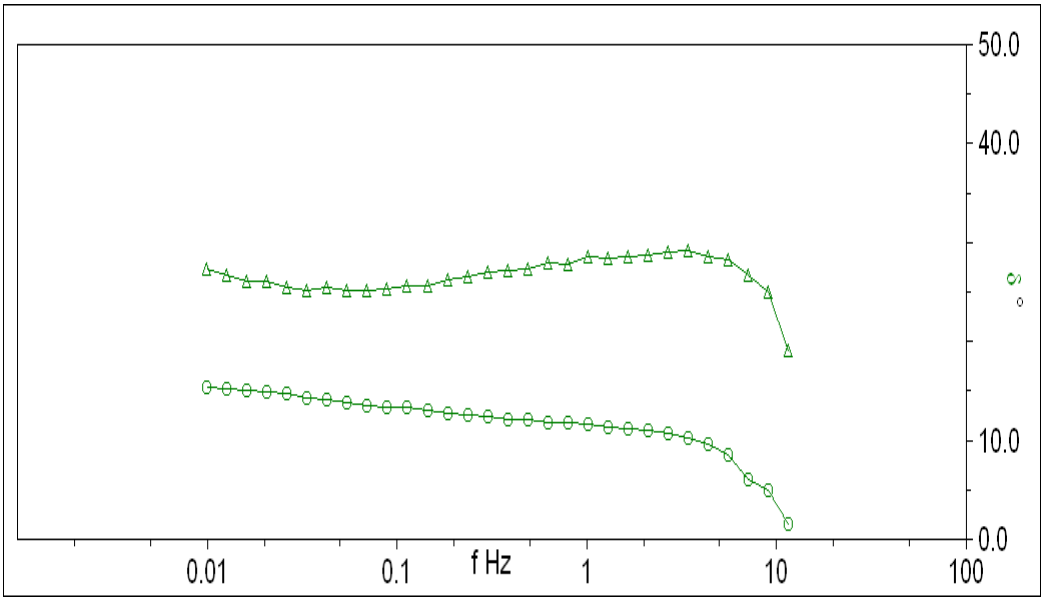

Figure 6.10. Influence of frequency on the phase angle (**δ**) of Xanthan Gum gels with Orphenadrine HCl. (O) 2% w/w gel, (Δ) 4% w/w gel.

However, the most apparent liquid-like behaviour was noted with the 4% w/w gel systems containing Orphenadrine HCl. These weak gel systems or slurries had phase angle values clearly higher than those obtained with 2% gel systems containing Orphenadrine HCl, indicating a more liquid like behaviour of the system. Slight variations were also apparent in the values of the phase angle for these systems with changes of the oscillation frequency, with values ranging between 25.0° and 28.5°.

The overall observation from oscillatory rheological studies indicates the formation of a weak three dimensional network, or gel structure, in blank Xanthan Gum, and Orphenadrine Citrate containing systems. The intensity or strength of such network is increased with the increase in the concentration of the gel system. Inclusion of the drug Orphenadrine HCl into the gel system seems to have a somewhat concentration dependent

effect; at the lower gel concentration of 2% w/w, the behaviour of Orphenadrine HCl containing gel systems was similar to that with blank Xanthan Gum and Orphenadrine Citrate containing systems. However, at higher concentrations, the influence of orphenadrine HCl seems to be more drastic resulting in a clear drop in the consistency of the gel structure.

6.2.1.2. Viscometric studies:

Viscometric studies were carried out on all gel systems. Such studies provide an insight into the behaviour of a gel at the point of breakdown of the structural consistency and beyond. Thus, the results of these studies would give an important comparison between the flow behaviour of all gel systems studied. Such behaviour could be directly related to the erosion process occurring on the outer surface of a hydrating hydrophilic matrix tablet.

Polymer particles usually undergo a continuous process of hydration within the gel layer of a hydrating matrix tablet. After reaching a certain concentration polymer chains usually break away and erode into the surrounding hydration medium. However, pharmaceutical tablets, including hydrophilic matrix ones, mostly contain a combination of soluble and in-soluble excipients in addition to the active ingredient. All of these materials could have a marked effect on the structural properties of the gel layer, either directly or by interacting with each other or with the polymer, leading in some cases to particle erosion from the outer region of the gel layer. Thus, viscometric studies would help in elucidating the

erosion and flow behaviour associated with the gel layer in the various tablets used in this study.

6.2.1.2.1. Investigating the flow behaviour of Xanthan Gum gels:

The influence of shear rate on the apparent viscosity (η) of blank and drug containing Xanthan Gum gels are documented below (Figures 6.11. to 6.13.). For blank Xanthan Gum gels a clear shear thinning behaviour is observed with gels prepared at all three concentrations (Figure 6.11.), which means a decrease in the apparent gel viscosity (η) with the increase in shear rate. Such an effect could be attributed mainly to the structural features of Xanthan Gum in the hydrated state; at lower shear rate values, Xanthan Gum molecules in their helical structures tend to aggregate and interact together by means of hydrogen bonding, whereas at higher values of shear rate the structural integrity of Xanthan Gum molecules is damaged and hydrogen bonds are broken and polymer molecules align in the shear direction leading to a drop in apparent viscosity. Similar trends were reported with gum solutions of lower concentrations (Rochefort and Middleman 1987, Zats and Knapp 1984).

An increase in the apparent viscosity (η) of blank Xanthan Gum gels is observed with the increase in gel concentration. Such behaviour could also be attributed to the structural properties of the hydrated Xanthan Gum molecules; increased gel concentration leads to the increase of hydrated Xanthan Gum molecules available for hydrogen bonding, thus increasing the rigidity of the system and giving rise to higher values of

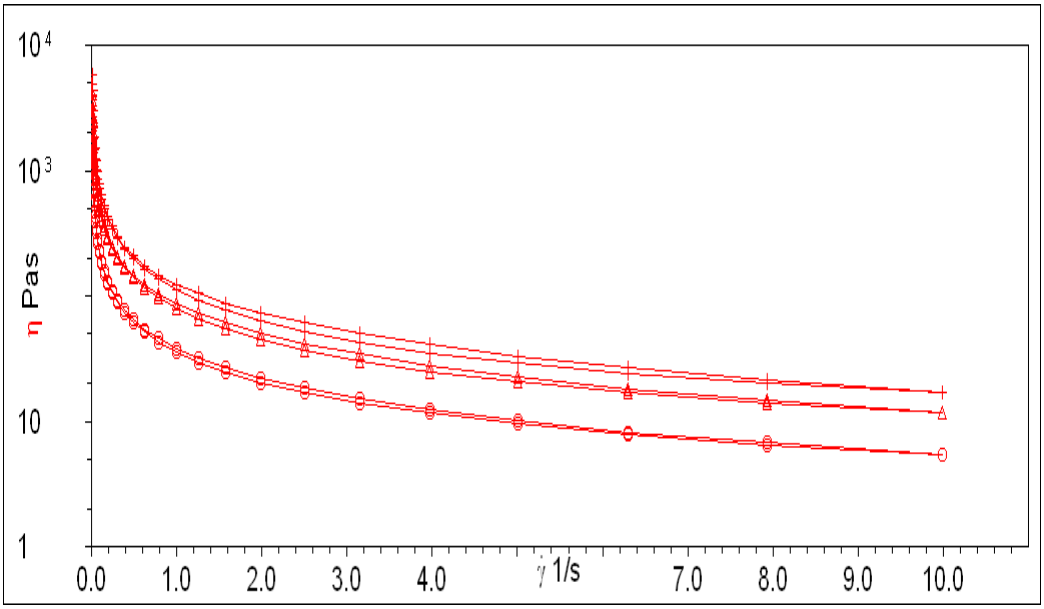

Figure 6.11. Influence of shear rate ($\dot{\gamma}$) on the apparent viscosity (η) of blank Xanthan Gum gels. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

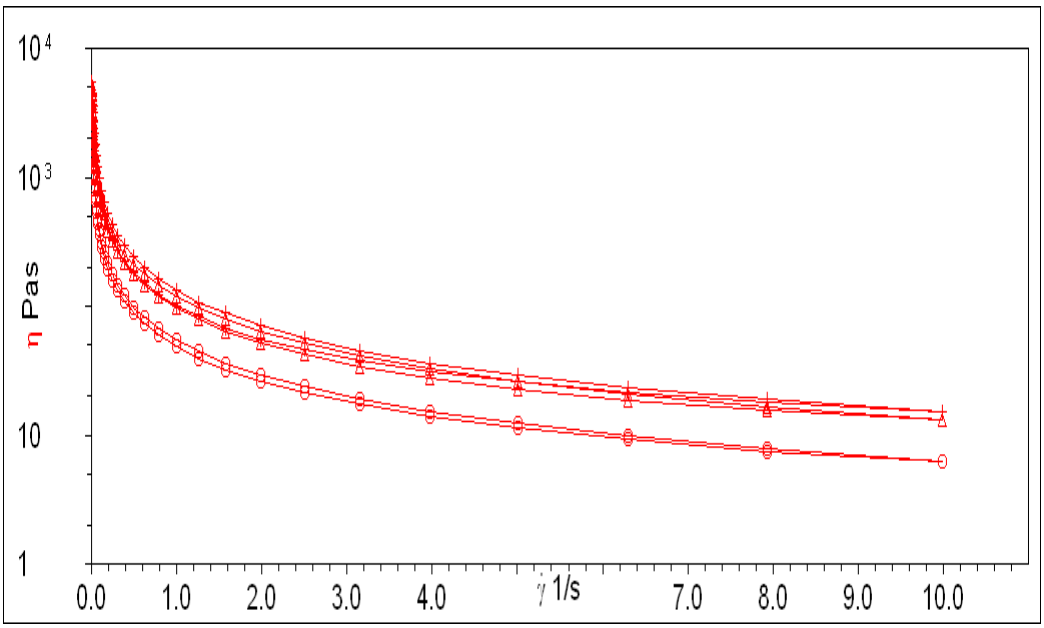

Figure 6.12. Influence of shear rate ($\dot{\gamma}$) on the apparent viscosity (η) of Xanthan Gum gels with Orphenadrine Citrate. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

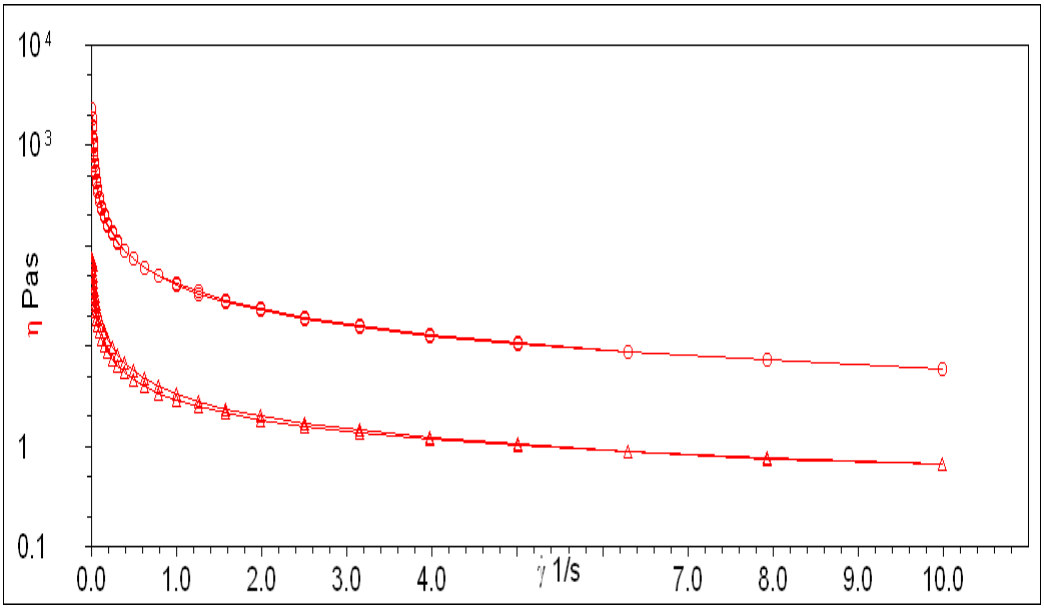

Figure 6.13. Influence of shear rate ($\dot{\gamma}$) on the apparent viscosity (η) of Xanthan Gum gels with Orphenadrine HCl. (O) 2% w/w gel, (Δ) 4% w/w gel.

apparent viscosity (η). The difference in the values of apparent viscosity (η) is more obvious between gels prepared at the lower concentration of 2% w/w and the ones prepared at the two higher concentratins of 4% and 6% w/w.

Incorporating the drug orphenadrine Citrate into the Xanthan Gum gels resulted in a similar shear thinning behaviour (Figure 6.12.). Moreover, the influence of increasing the concentration of the gel is similar to that observed with blank Xanthan Gum gels, where a progressive increase in gel apparent viscosity (η) was observed with the increase in gel concentration. A slightly smaller difference was observed between the apparent viscosity (η) of gels prepared at concentrations of 4% and 6% w/w, as compared to blank Xanthan Gum gels.

Incorporating the drug Orphenadrine HCl into Xanthan Gum gels resulted in a concentration dependent effect (Figure 6.13.); at the lower gel concentration of 2% w/w, the profile of apparent gel viscosity (η) with shear rate was similar to those of blank and Orphenadrine Citrate containing gels. Upon further increase in gel concentration to 4% w/w, a clear drop in gel apparent viscosity (η) was noted. Such behaviour is in agreement with the results of the dynamic oscillatory studies conducted on these gels. This behaviour could arise from the inability of the Xanthan Gum molecules to fully hydrate and interact by hydrogen bonding leading to the formation of a weaker three dimensional network of gel structure. However, the presence of a shear thinning behaviour associated with such system (Figure 6.13) indicates that some kind of structural integrity is still found in the system, which indicates that the influence of the drug had not diminished the ability of Xanthan Gum molecules to interact and form a three dimensional network.

The dependence of the shear stress on the shear rate for blank and drug containing Xanthan Gum gels is shown in the flow curves of such systems (Figures 6.14. to 6.16.). For blank Xanthan Gum gels (Figure 6.14.), two main features are apparent from the flow curves associated with the gels. Initially, it is clear that all gels exhibit some kind of yield stress which is the minimum stress or force required to break the gel structure, as the values of the shear stress are consistently higher than zero at the lower values of shear rate. The value of the yield stress becomes progressively higher with the increase in gel concentration.

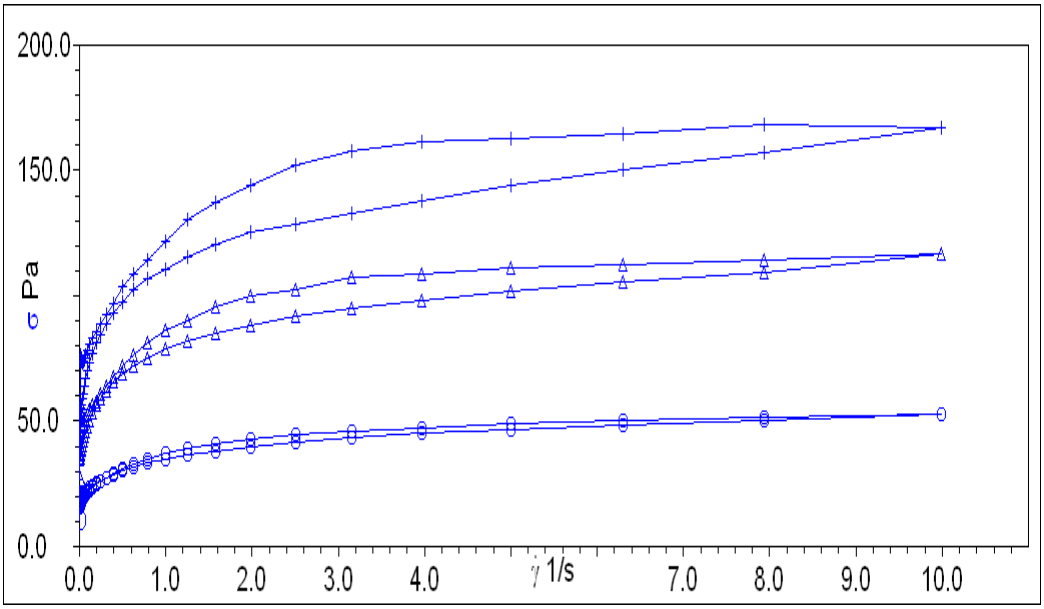

Figure 6.14. Flow Curves of blank Xanthan Gum gels. ($\dot{\gamma}$) is shear rate, and (σ) is shear stress. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

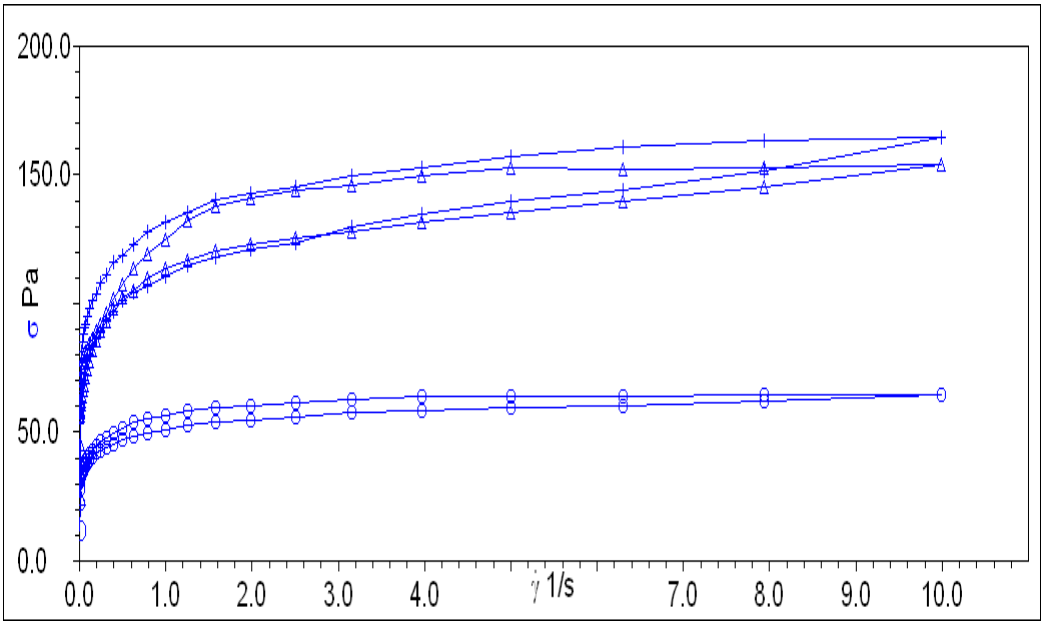

Figure 6.15. Flow Curves of Xanthan Gum gels with Orphenadrine Citrate. ($\dot{\gamma}$) is shear rate, and (σ) is shear stress. (O) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

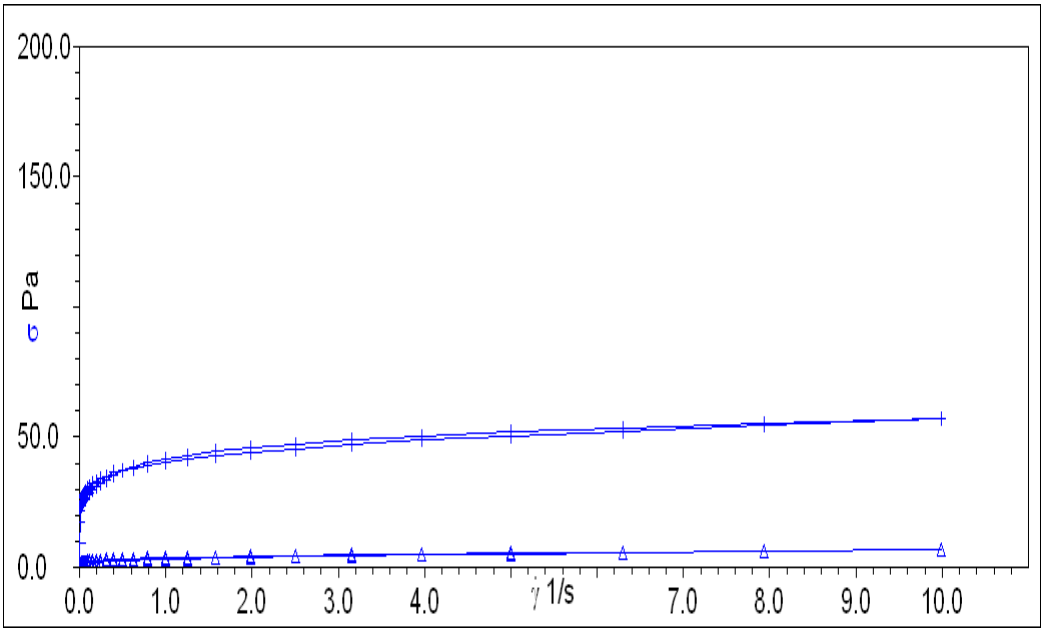

Figure 6.16. Flow Curves of Xanthan Gum gels with Orphenadrine HCl. ($\dot{\gamma}$) is shear rate, and (σ) is shear stress. (O) 2% w/w gel, (Δ) 4% w/w gel.

This effect, once again is related to the interaction between the hydrated Xanthan Gum molecules and the need to apply a certain level of stress to break such interactions.

Another aspect that becomes clear from the flow curves of blank Xanthan Gum gels, is the thixotropic behaviour associated with such systems. Thixotropy could be defined as the decrease in the apparent viscosity, of the gel systems in this study, under constant shear stress or shear rate which is followed by a process of gradual recovery when such shear stress or shear rate is removed. Moreover this effect is time dependent (Barnes et al 1996). In the case of gels, Thixotropy could be indicative of the breakdown of the gel structure upon application of stress over time, and the consecutive rebuilding or reformation of gel structure upon removal of the affecting stress.

Quantitative insight into the magnitude of thixotropic behaviour was accomplished by integrating the area of the “hysteresis loop” which is the area between the “up” and “down” segments of the flow curve. The results of the thixotropic behaviour of all blank and drug containing gel systems are listed in Table 6.1. For Blank Xanthan Gum gels, an increase in thixotropy is observed with the increase in gel concentration. This could be attributed to the larger number of hydrogen bonding interactions in the structural network of gels with higher concentrations, which, upon destruction, would cause a more apparent drop in gel structural integrity. Moreover, such systems would require more time to rebuild their structural networks after the removal of the affecting stress.

Gels containing the drug Orphenadrine Citrate (Figure 6.15.) exhibited a similar behaviour in terms of the presence of a yield stress value. However, such gels exhibited a higher degree of thixotropic behaviour as compared to blank Xanthan Gum gels (Table 6.1.). Such change in behaviour could be attributed to a number of factors. Initially, Orphenadrine Citrate has an aqueous solubility of 1 in 70 of water(Moffat et al 2004). Thus a certain fraction of drug particles could remain suspended within the gel network formed by Xanthan Gum leading to a change in the rigidity of the network. Secondly, upon dissolution, Orphenadrine is a cationic drug and has the potential to interact with the anionic Xanthan Gum. Such interaction could lead to the formation of a complex with limited or low aqueous solubility, which in turn could influence the properties of the gel network. A pattern, similar to that

obtained with blank Xanthan Gum gels, is apparent in terms of the influence of gel concentration on the thixotropic behaviour; gels produced at higher concentrations had higher degrees of thixotopic behaviour (Table 6.1.).

	Gel Concentraion (%w/w)		
Gel Type	2%	4%	6%
Blank Xanthan Gum	21.785 (2.805)	74.466 (2.215)	144.323 (1.422)
Xanthan Gum with Orphenadrine Citrate	32.235 (2.017)	101.919 (4.125)	155.950 (8.788)
Xanthan Gum with Orphenadrine HCl	8.376 (3.700)	1.626 (0.647)	n.d. n.d.

Table 6.1. Thixotopy values for blank and drug containing Xanthan Gum gels, (SD) n=3. (n.d.: not determined, see section 6.2.1.).

Gels containing the drug Orphenadrine HCl exhibited consistently lower values of thixotropic behaviour as compared to blank and Orphenadrine Citrate containing gels. Moreover, and in agreement with the results of dynamic studies, a drop in the degree of thixotropic behaviour was observed with the increase of gel concentration from 2% w/w to 4% w/w, which is attributed to the lower degree of structural integrity and interaction. In terms of yield stress values, Orphenadrine HCl containing gels at a concentration of 2% w/w exhibited a certain degree of yield stress similar to that exhibited by blank gels. However, gels with a concentration of 4%, seem to exhibit a diminishing value of yield stress.

In order to further elucidate the influence of gel concentration on the extent of thixotropic behaviour associated with the various gels, analysis of variance (ANOVA) was carried out to determine the presence and nature of any significant effect of concentration on thixotropic behaviour.

For blank Xanthan Gum gels, analysis of variance (ANOVA) indicated a significant influence of the concentration of the gel on its thixotropic behaviour ($F= 2298.469$, $p < 0.001$). Post hoc analysis was carried out using the Sheffé test to elucidate the difference between the three levels of gel concentration. The results of the analysis are shown below (Table 6.2.) and they indicate a significant difference between all thee levels of gel concentration in terms of the extent of their thixotropic behaviour.

Scheffe

		Subset		
Conc	N	1	2	3
2%	3	21.78533		
4%	3		74.46633	
6%	3			144.32333
Sig.		1.000	1.000	1.000

*Alpha = .05.

Table 6.2. Post hoc analysis results for thixotopy values of blank Xanthan Gum gels. (The values reported are the mean thixotropy values, and the classification into different subsets is used to indicate significant differences between mean values).

A similar pattern was noted with Orphenadrine Citrate containing gels; the result of the analysis of variance (ANOVA) indicated a significant effect of the change of gel concentration on the extent of their thixotopic behaviour ($F= 352.148$, $p < 0.001$). Post hoc analysis, using the Sheffé test (Table 6.3.), indicated a significant difference between all thee levels of gel concentration in terms of the extent of their thixotropic behaviour.

Scheffe

		Subset		
Conc	N	1	2	3
2%	3	32.23467		
4%	3		101.91933	
6%	3			155.95000
Sig.		1.000	1.000	1.000

* Alpha = .05.

Table 6.3. Post hoc analysis results for thixotopy values of Xanthan Gum gels with Orphenadrine Citrate, (see table 6.2. for further explanation).

For gels containing the drug Orphenadrine HCL, only two levels of gel concentration were investigated, hence, the independent sample t-test method was used to elucidate the presence of any significant difference between the values of thixotropic behaviour associated with the two concentrations. The results indicated that no significant difference was found between the values of the thixotropic behaviour associated with the two concentrations ($t= 3.113$, $p= 0.083$.).

6.2.1.2.2. Determination of the yield stress of Xanthan Gum gels.

An experimental approach was adopted for the determination of the yield stress values associated with the various gels used in this study. This method includes the application of progressively increasing shear stress values on the samples, with continuous monitoring of the strain and the instantaneous viscosity within the samples. Upon reaching the yield value of the sample, a clear deflection is noted in the values of both monitored variables due to the destruction of the structural integrity of the gel system. This method provided a rather practical and reliable method for the determination of the actual yield stress values associated with gel samples.

The results of yield stress determination studies for blank and drug containing Xanthan Gum gels are presented in Figures 6.17 to 6.20. and in Table 6.4. For blank Xanthan Gum gels (Figure 6.17.) and (Table 6.4.) a progressive increase in the yield stress values is observed with the increase in gel concentration.

A rather similar pattern is observed with gels containing the drug Orphenadrine Citrate (Figure 6.18.) and (Table 6.4.). At the two lower concentrations of 2% and 4% w/w, such gels exhibited yield stress values higher than those exhibited by blank Xanthan Gum gels with similar concentration. However, a different observation was noted for the yield stress at higher concentration. After an initial increase in the yield stress values, a drop is observed in these values with further increase in gel

concentration to 6% w/w. This behaviour could be attributed to the possible presence of undissolved free drug particles or drug-polymer complex particles within the gel structure which could enhance gel breakage and lower the yield value when present at higher concentrations.

Gels with a concentration of 2% w/w and containing the drug Orphenadrine HCl (Figure 6.19.) and (Table 6.4.), exhibited yield stress values similar to those obtained with blank Xanthan Gum gels. Further increase in gel concentration to 4% w/w, (Figure 6.20.) and (Table 6.4.), resulted in a marked drop in yield stress values.

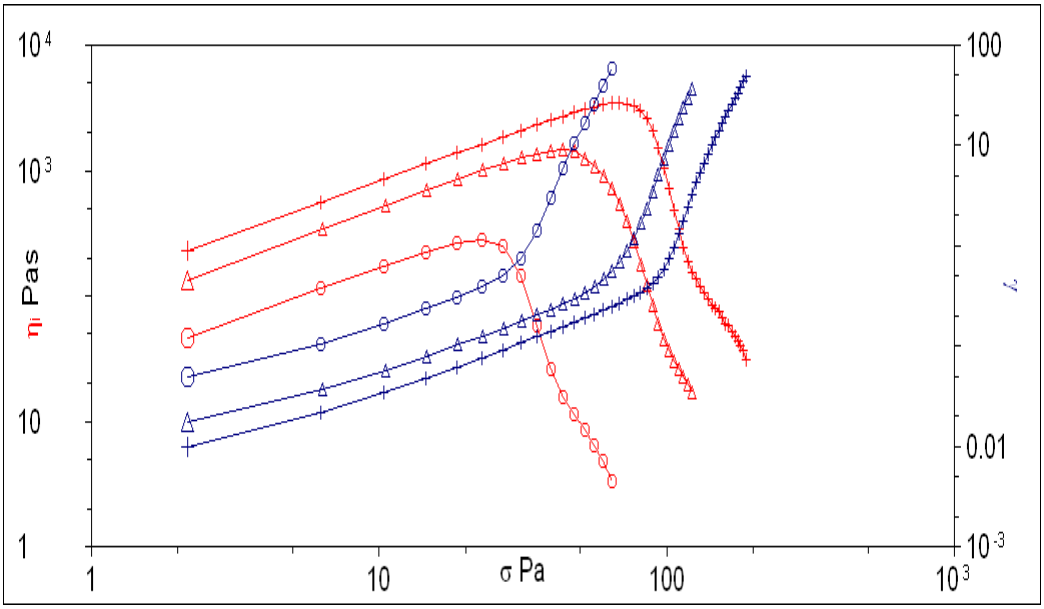

Figure 6.17. Yield stress determination for blank Xanthan Gum gels. (**σ**) is the shear stress, blue curves are the strain (**γ**), and red curves are the instantaneous viscosity (η_i). (**O**) 2% w/w gel, (Δ) 4% w/w gel, and (**+**) 6% gel.

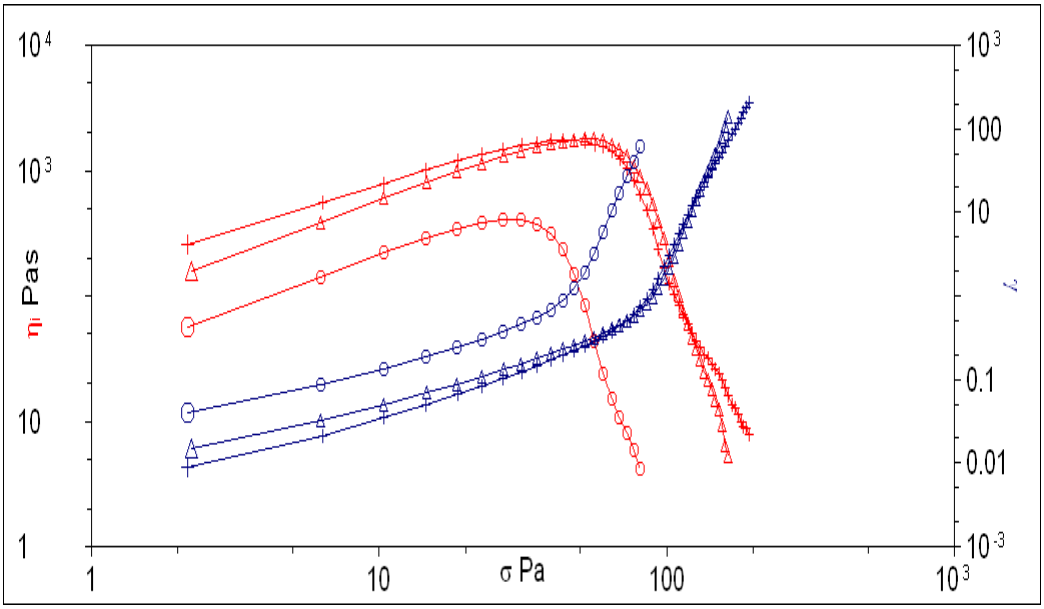

Figure 6.18. Yield stress determination for Xanthan Gum gels with Orphenadrine Citrate. (**σ**) is the shear stress, blue curves are the strain (**γ**), and red curves are the instantaneous viscosity (η_i). (**O**) 2% w/w gel, (Δ) 4% w/w gel, and (+) 6% gel.

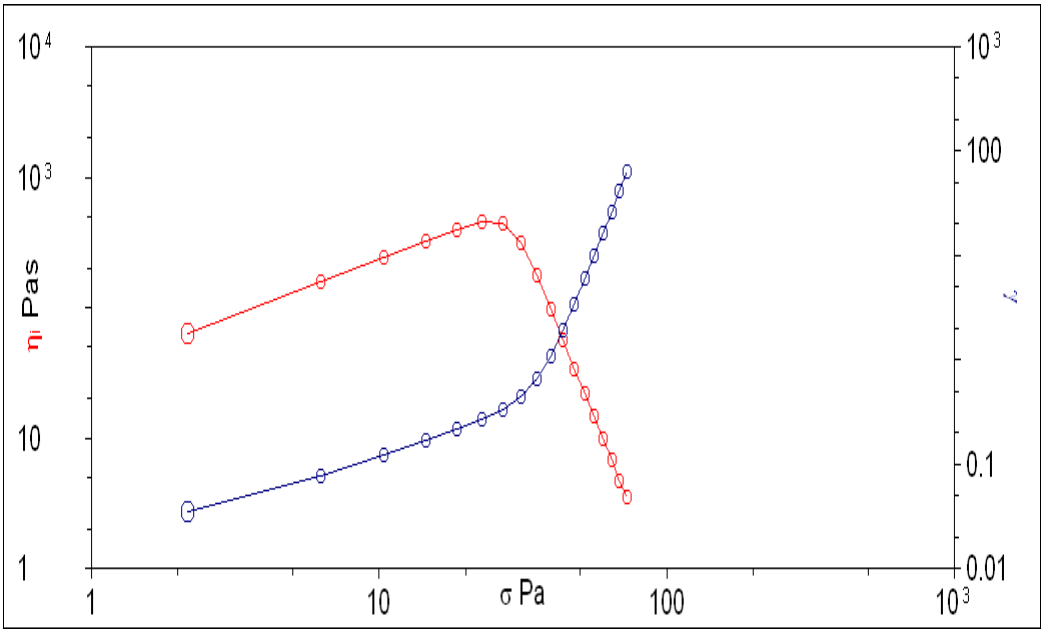

Figure 6.19. Yield stress determination for 2% w/w Xanthan Gum gels with Orphenadrine HCl. (**σ**) is the shear stress, blue curves are the strain (**γ**), and red curves are the instantaneous viscosity (η_i).

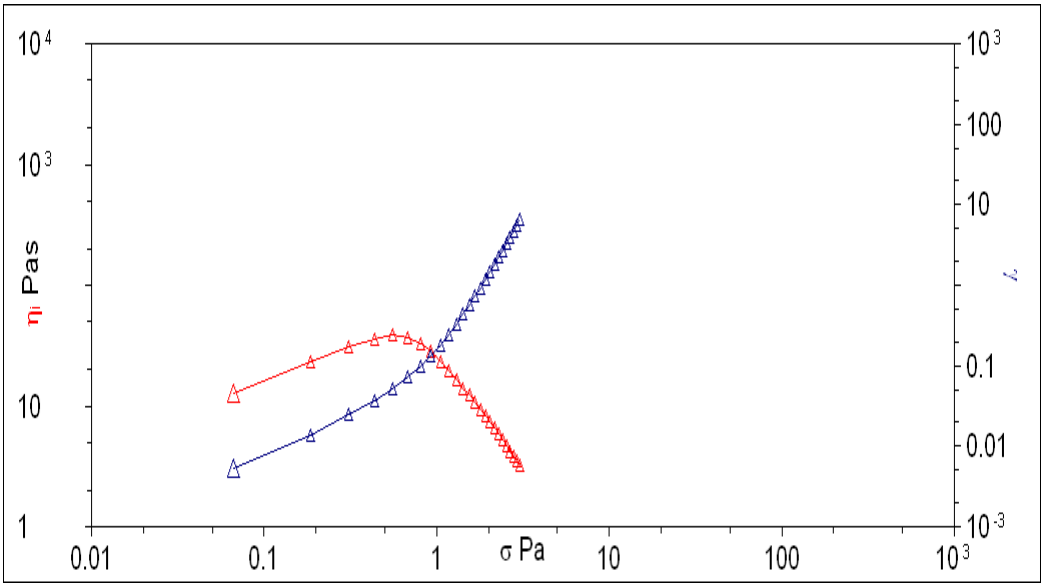

Figure 6.20. Yield stress determination for 4% w/w Xanthan Gum gels with Orphenadrine HCl. (**σ**) is the shear stress, blue curves are the strain (**γ**), and red curves are the instantaneous viscosity (η_i).

	Gel Concentraion (%w/w)		
Gel Type	2%	4%	6%
Blank Xanthan Gum	20.199 (2.366)	42.456 (2.366)	60.456 (4.096)
Xanthan Gum with Orphenadrine Citrate	27.140 (0.080)	52.127 (0.080)	43.798 (4.165)
Xanthan Gum with Orphenadrine HCl	20.199 (2.366)	0.730 (0.191)	n.d. n.d.

Table 6.4. Yield stress values for blank and drug containing Xanthan Gum gels, (SD) n=3, (n.d.: not determined, see section 6.2.1.).

Statistical analysis using analysis of variance (ANOVA) was carried out to elucidate the difference between the yield stress values of the different gel systems. For blank Xanthan Gum gels, the results of the analysis of variance (ANOVA) indicated a significant influence of gel concentration on the yield value ($F= 130.875$, $p < 0.001$). Post hoc analysis using the Sheffé test (Table 6.5.) revealed a significant difference in the yield stress values obtained with all three levels of gel concentration.

For gels containing the drug Orphenadrine Citrate, a similar observation was noted. The results of the ANOVA indicated a significant influence on the gel yield stress values as a result of the change in gel concentration ($F= 83.909$,$p < 0.001$). The results of the post hoc Sheffé test (Table 6.6.) indicated a significant difference between the yield stress values of all three levels of gel concentration.

Scheffe

		Subset		
Conc	N	1	2	3
2%	3	20.19867		
4%	3		42.45633	
6%	3			60.45633
Sig.		1.000	1.000	1.000

* Alpha = .05.

Table 6.5. Post hoc analysis results for yield stress values of blank Xanthan Gum gels. (The values reported are the mean yield stress values, and the classification into different subsets is used to indicate significant differences between mean values).

Scheffe

Conc	N	Subset 1	Subset 2	Subset 3
2%	3	27.14000		
6%	3		43.79800	
4%	3			52.12733
Sig.		1.000	1.000	1.000

* Alpha = .05.

Table 6.6. Post hoc analysis results for yield stress values of Xanthan Gum gels with Orphenadrine Citrate, (see table 6.5. for further explanation)

The results of the independent sample t-test for 2% and 4% w/w gels containing the drug Orphenadrine HCl, indicated a significant difference between the yield values of the two levels of gel concentration (t= 14.209, p= 0.005).

6.2.2. Thermal investigation of dried Xanthan Gum gel systems:

The results of the rheological studies indicated a change in the gel properties of Xanthan Gum, caused by the addition of both drugs; Orphenadrine Citrate, and more significantly, Orphenadrine HCl. Such behaviour could, in part, be the result of the potential ionic interaction between the anionic Xanthan Gum and the cationic Orphenadrine. Thus, thermal investigation studies were carried out for the various gel systems studied, and also for dry polymer and drug powders, and powder

mixtures. This was done to get further insight into the physicochemical properties associated with the various samples.

Temperature modulated differential scanning calorimeter (TMDSC) is an advanced thermal characterisation technique. It provides a major advantage over conventional differential scanning calorimetry (DSC) due to its ability to separate the thermal heat flow signal associated with each sample into its reversing and non-reversing components. Thus it facilitates the characterisation of the various thermal behaviour patterns occurring within the sample (Verdonck et al 1999)

6.2.2.1. Pure polymer and drug powders:

The temperature modulated thermograms for the pure powders of the polymer and drugs used in this study are shown in Figures 6.21. to 6.23., respectively. For Xanthan Gum (Figure 6.21.), one main feature is apparent from the thermogram; a broad endotherm is clearly apparent in both the overall heat flow and the non-reversing heat flow signals and peaks at 100°C. Such broad endotherm is usually associated with moisture loss from the polymer lattice. Similar results were reported with other hydrophilic polymers such as Hydroxypropyl Methylcellulose (Ford 1999). The position of such endotherm is highly dependent on the encapsulation technique used in sample preparation, where more sealed pan types like hermetically sealed ones could slow the process of moisture loss and shifts the endotherm upwards (Ford 1999).

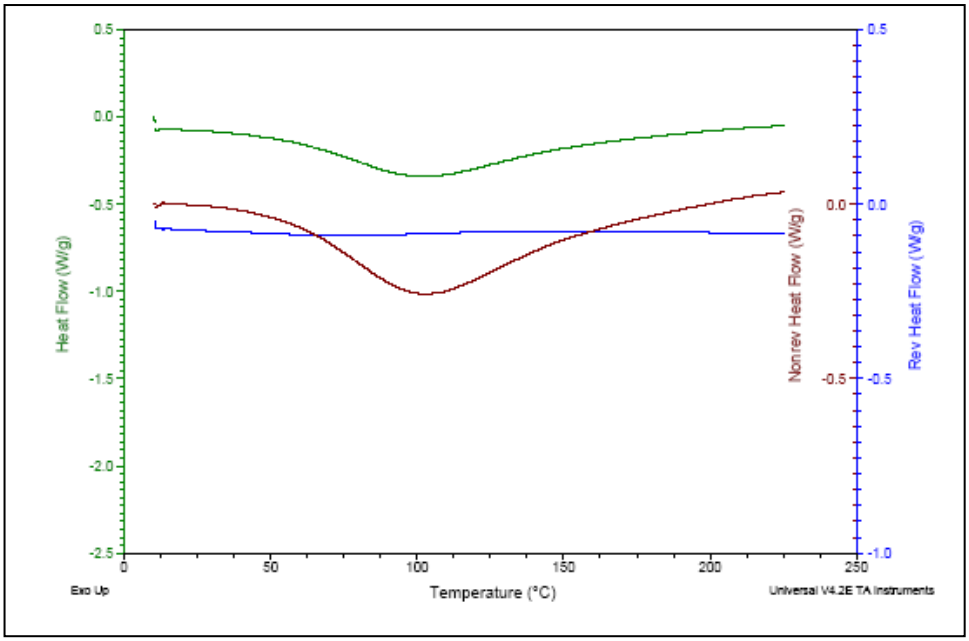

Figure 6.21. Temperature modulated thermogram of Xanthan Gum powder, sample weight 4.8 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

The glass transition temperature, i.e. the temperature at which phase transition in the polymer structure from the glassy state to the rubbery state occurs is often present in the form of a stepwise decline in the reversing heat flow signal. However, no glass transition pattern is clearly apparent in the thermogram of Xanthan Gum powder. The determination of such behaviour in hydrophilic polymers is often difficult, as the magnitude of moisture in the sample, and the subsequent loss of such water during the heating process, could cause significant changes in the shape and shifts in the position of the glass transition pattern. Furthermore, the presence of moisture in the polymer lattice could

broaden the range over which glass transition takes place (Joshi and Wilson 1993, Ford 1999).

The thermogram of pure Orphenadrine Citrate powder (Figure 6.22.) shows a distinctive sharp endothermic peak in all of the heat flow signals at about 136°C. Such peak is usually associated with powder melting. The finding is in agreement with previously reported reference values of 137°C (BP 2007). Another endothermic peak is apparent at a higher temperature of 170°C. The occurrence of such peak in the overall heat flow signal and in the non-reversing heat flow signal is indicative of a dehydration process which is typically expected after powder melting.

A similar pattern is observed in the thermogram of pure Orphenadrine HCl powder (Figure 6.23.). A sharp endothermic peak is apparent in all heat flow signals at about 160°C. This is indicative of powder melting, and is in agreement with the previously reported reference value of 160°C (BP 2007). Furthermore, a broad dehydration endotherm is apparent in the non-reversing heat flow signal and in the overall heat flow signal between 180°C and 225°C, indicating a process of sample dehydration.

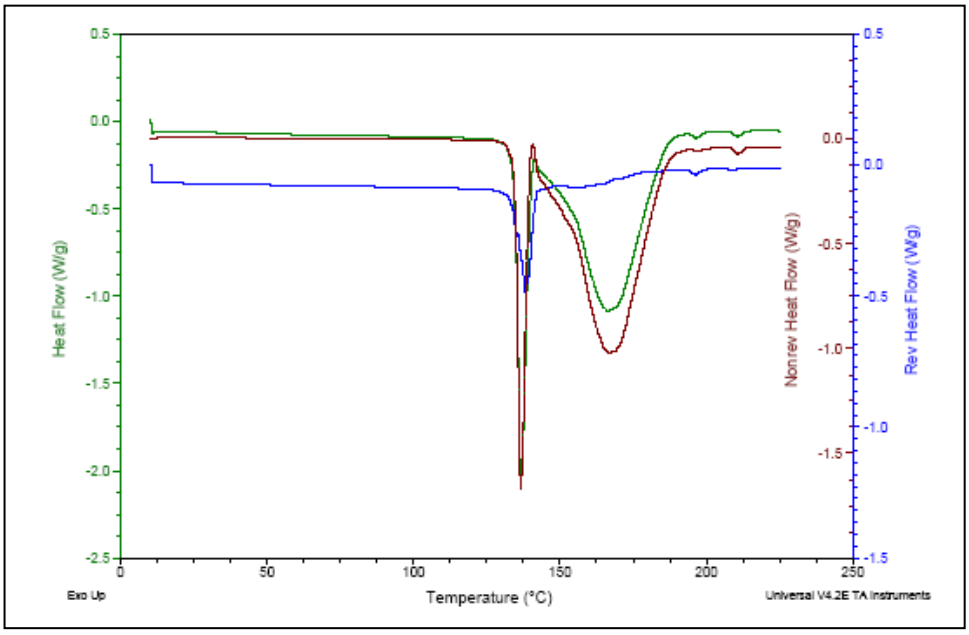

Figure 6.22. Temperature modulated thermogram of Orphenadrine Citrate powder, sample weight 4.6 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

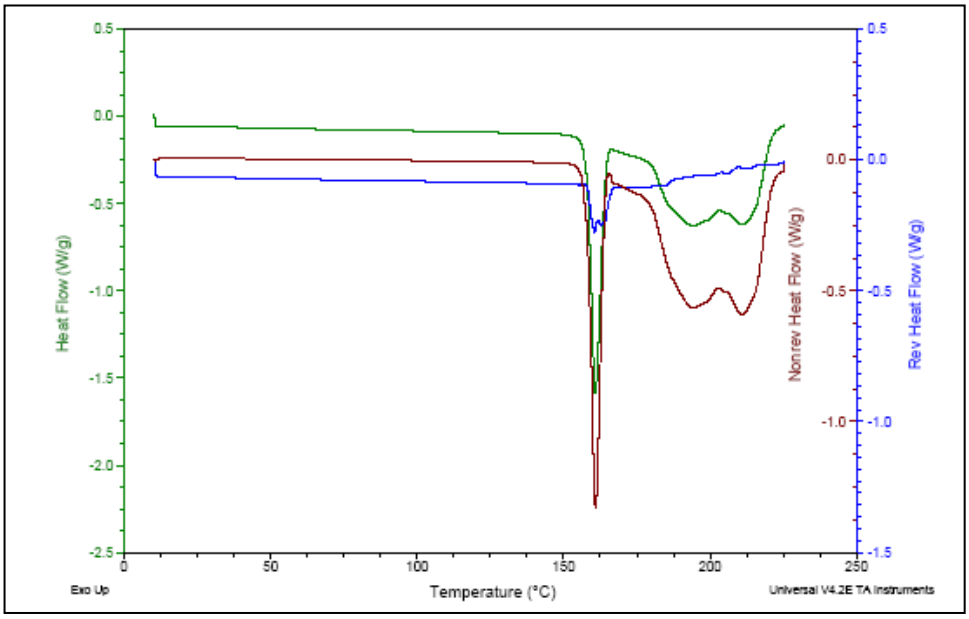

Figure 6.23. Temperature modulated thermogram of Orphenadrine HCl powder, sample weight 4.9 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

6.2.2.2. Polymer-drug physical mixtures:

Temperature modulated thermograms for physical powder mixtures containing Xanthan Gum and either of the two drugs are presented in Figures 6.24. and 6.25. The thermogram of the physical mixture between Xanthan Gum and Orphenadrine Citrate (Figure 6.24.) appears to contain the combined thermal patterns of both entities. An endotherm is apparent in all heat flow signals at a temperature of 136°C. Such endotherm is comparable to the endotherm associated with the melting point of Orphenadrine Citrate (Figure 6.22.). A broad endotherm is observed in both the total and the non-reversing heat flow signals between 50°C and 140°C and this could be in turn attributed to the loss of moisture from the hydrophilic Xanthan Gum. Two more endothermic peaks are apparent in the total and the non-reversing heat flow signals at 175°C and 200°C respectively, and such behaviour probably arises from the dehydration process associated with the melted drug powder.

A similar pattern is observed in the thermogram of the physical mixture containing Xanthan Gum and the drug Orphenadrine HCl. A melting endotherm is observed with a peak at 160°C, corresponding to the melting point of Orphenadrine HCl. A broad dehydration endotherm is apparent in both the total and non-reversing heat flow signals between 25°C and 150°C indicative of moisture loss from Xanthan Gum. Finally an endotherm with multiple peaks is apparent in both the total and non-reversing heat flow signals between 160°C and 200°C, probably associated with dehydration of the melted drug.

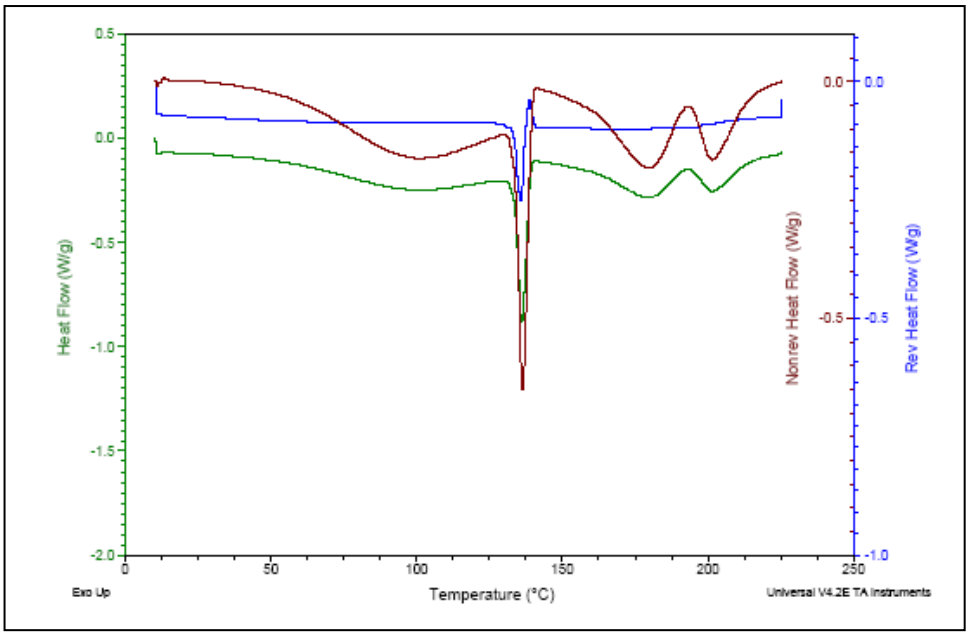

Figure 6.24. Temperature modulated thermogram of Xanthan Gum-Orphenadrine Citrate physical mixture, sample weight 5.2 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

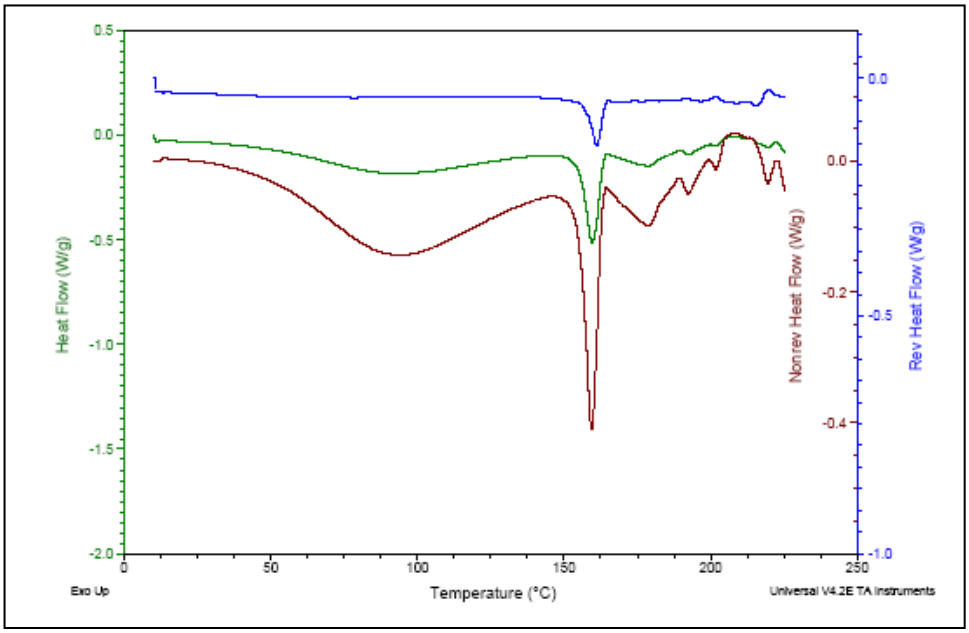

Figure 6.25. Temperature modulated thermogram of Xanthan Gum-Orphenadrine HCl physical mixture, sample weight 5.2 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

The presence of melting peaks in the physical mixtures containing both drugs, and the similarity between the positioning of such peaks with the melting peaks detected for the pure drug powders, indicate the presence of both drugs in their crystalline state within the mixtures. Thus, no significant interaction or complex formation is apparent between Xanthan Gum and either drug in the solid state.

6.2.2.3. Polymer-drug dried gel samples:

Gel samples used for thermal characterisation were subjected to a multiple drying process, encompassing oven drying, and further dehydration using silica gel. The drying process was carried out in accordance with the main objective sought from these studies, i.e. investigating any potential interaction between Xanthan Gum and either of the two drugs used in this study. Such interaction, if present, could be detected more clearly by monitoring the melting signal associated with the drugs in the dried films.

6.2.2.3.1. Dried blank Xanthan Gum gels:

Dried gel samples prepared using Xanthan Gum alone (Figures 6.26 to 6.28) exhibited a thermal behaviour similar to that exhibited by Xanthan Gum powder (Figure 6.21.). The characteristic broad endotherm at lower temperatures is present in the total and non-reversing heat flow signals of gels prepared at all three concentrations. No significant thermal patterns are observed in the reversing heat flow signal of any of the gels. The lack of difference between the gels prepared at different concentrations could

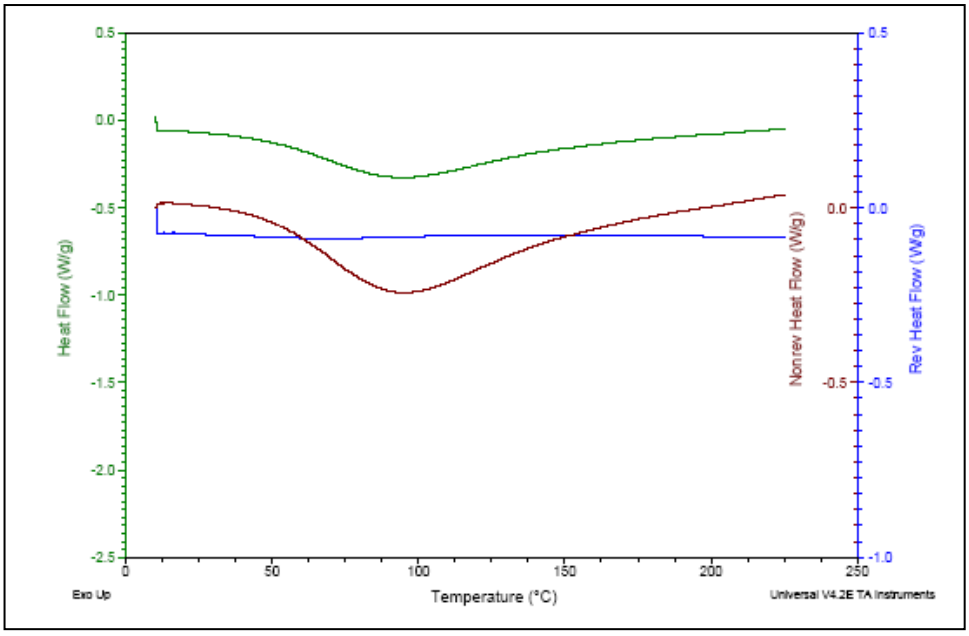

Figure 6.26. Temperature modulated thermogram of dried Xanthan Gum gel, concentration 2% w/w, sample weight 4.9 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

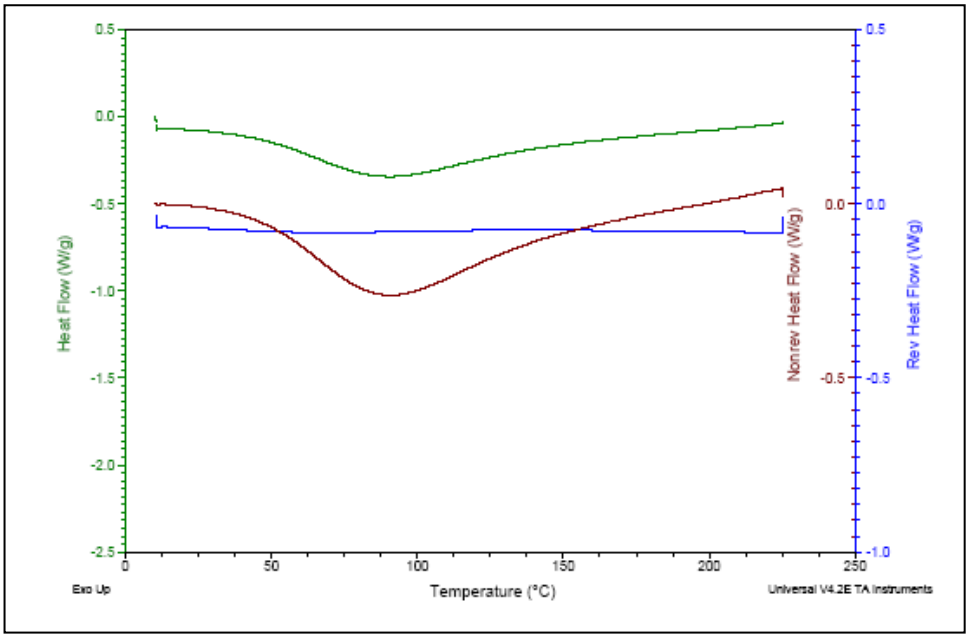

Figure 6.27. Temperature modulated thermogram of dried Xanthan Gum gel, concentration 4% w/w, sample weight 5.0 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

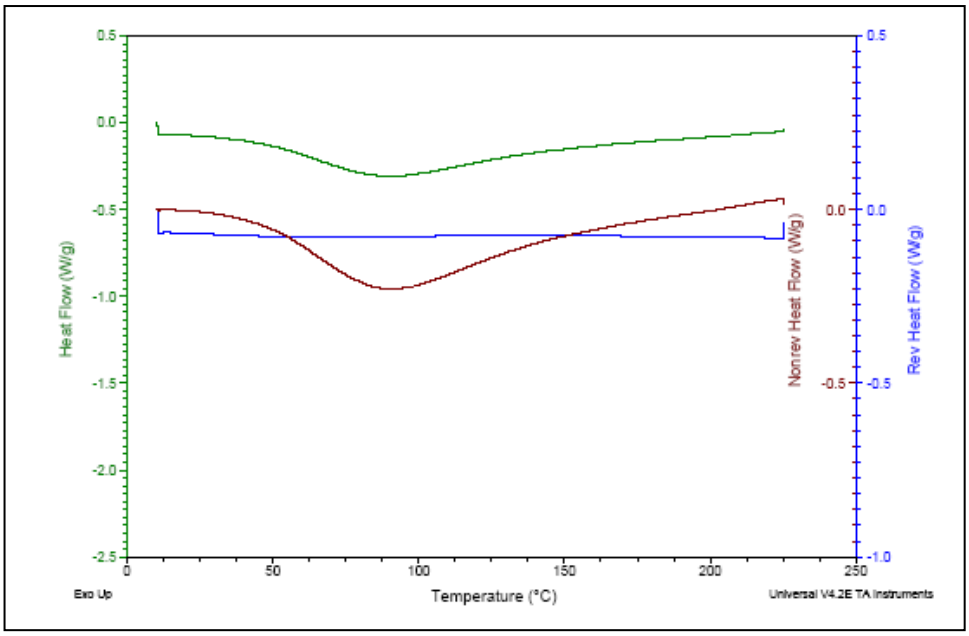

Figure 6.28. Temperature modulated thermogram of dried Xanthan Gum gel, concentration 6% w/w, sample weight 4.7 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

be attributed to the drying process utilised in this study; the final sample weight used in the thermal investigation of the samples comprised mainly of polymer molecules. Moreover, the same polymer batch was used in the preparation of all gel samples, thus no chemical differences are present between samples in terms of their polymer content.

6.2.2.3.2. Dried Xanthan Gum gels with added drugs:

The thermograms of Xanthan Gum gels containing Orphenadrine Citrate and Orphenadrine HCl are presented in Figures (6.29. to 6.31.) and Figures (6.32. to 6.34.) respectively. The main Observation noted in all thermograms is the lack of drug melting endotherms from the reversing heat signal of any of the gel samples studied. Such endotherm is usually

associated with the presence of the crystalline form of the drugs in the dried gel structure. Such behaviour is indicative of the presence of the drugs in the amorphous state, and this is highly associated with the interaction between Xanthan Gum and both salts of Orphenadrine used. Upon hydration of the gels, the anionic groups present mainly on the side chains of Xanthan Gum molecules, namely pyruvate and acetate, become ionised and have the potential to interact with the ionised cationic Orphenadrine molecules to form a complex which could differ in its physicochemical properties from the Orphenadrine salts used. Similar observations of drug-polymer ionic interaction and their effect on the thermal behaviour of either entities were previously reported (Yuksel et al 1996, Takka 2003).

The lack of any melting endotherm in the thermal behaviour of gels prepared using both drugs indicates that both the highly soluble Orphenadrine HCl and the sparingly soluble Orphenadrine Citrate underwent interaction with Xanthan Gum upon hydration.

The thermograms of Xanthan Gum gels containing the drug Orphenadrine Citrate (Figures 6.29. to 6.31.) exhibited two broad endotherms, noted in the total heat flow and the non-reversing heat flow signals. The first endotherm which peaked at around 80°C could be attributed to the loss of moisture from the hydrophilic Xanthan Gum,

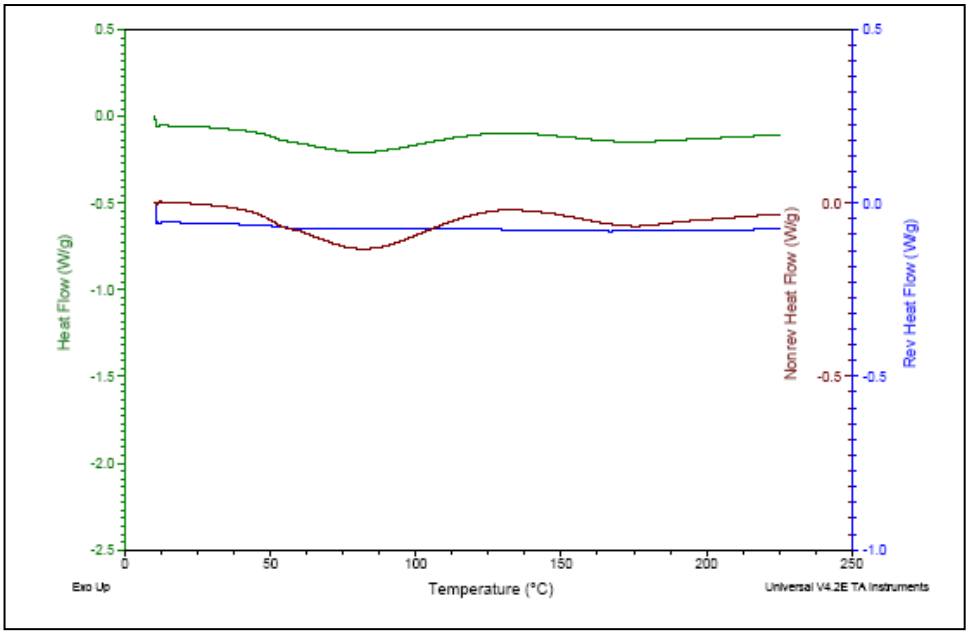

Figure 6.29. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine Citrate, concentration 2% w/w, sample weight 5.4 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

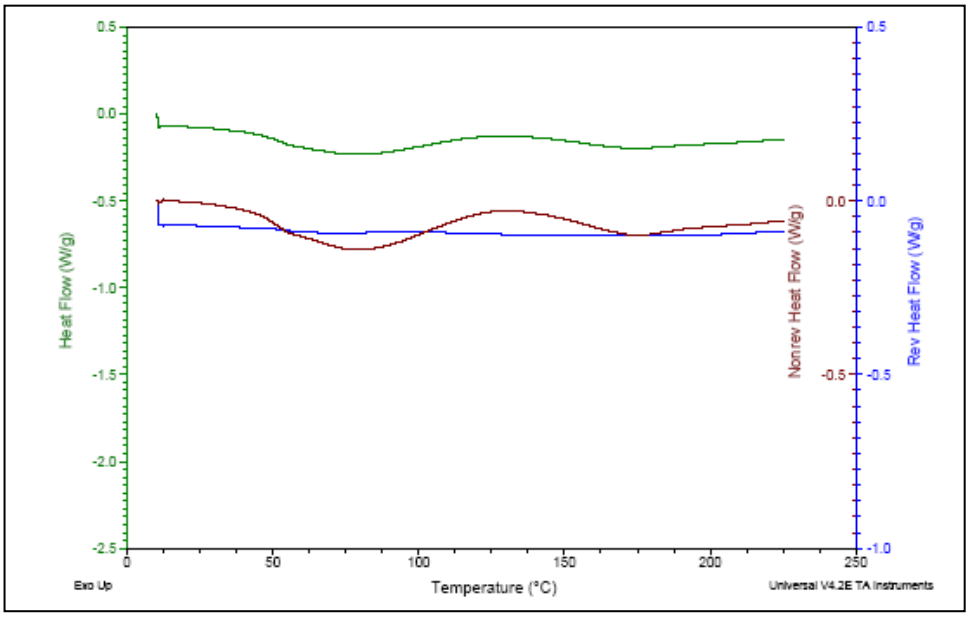

Figure 6.30. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine Citrate, concentration 4% w/w, sample weight 5.0 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

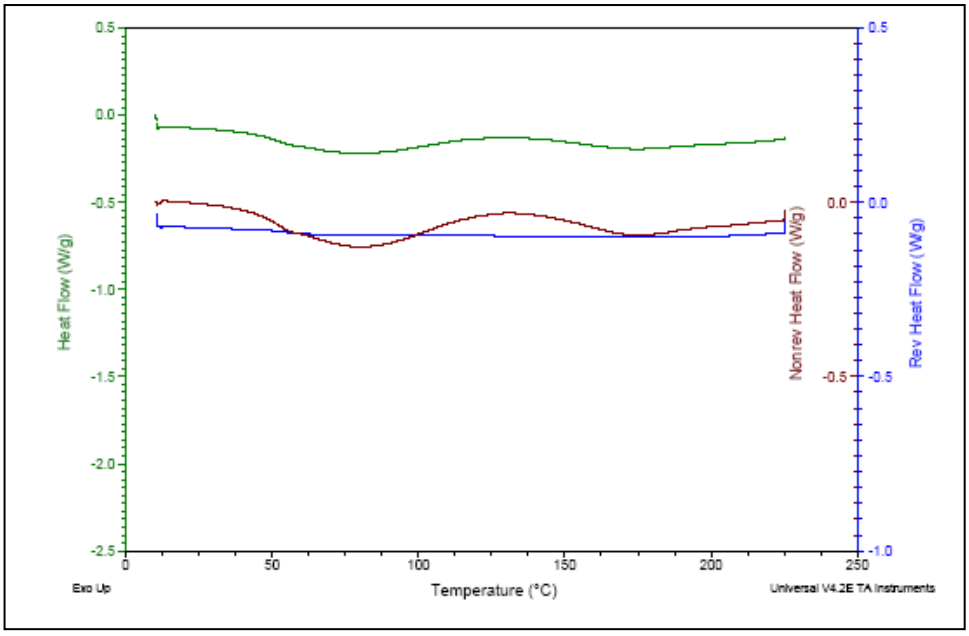

Figure 6.31. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine Citrate, concentration 6% w/w, sample weight 4.6 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

whereas, the second endotherm occurred at a much higher temperature, and peaked at around 225°C.

Thermograms of Xanthan Gum gels containing the drug Orphenadrine HCl (Figures 6.32. to 6.34.) exhibited the presence of one main endothermic peak in both the total heat flow and the non-reversing heat flow signals. The positioning of this endotherm at lower temperatures with a peak around 80°C is once again indicative of its correlation with moisture loss from the hydrophilic Xanthan Gum. No other endotherm is apparent in the thermograms of these gels which could indicate a difference in the interaction pattern between Xanthan Gum and either of the two drugs.

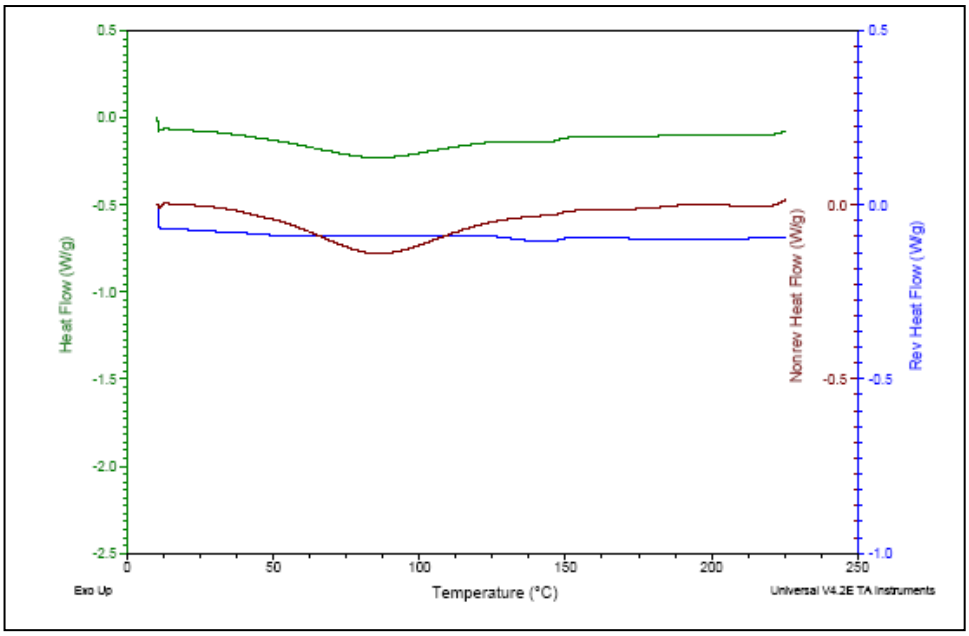

Figure 6.32. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine HCl, concentration 2% w/w, sample weight 4.7 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

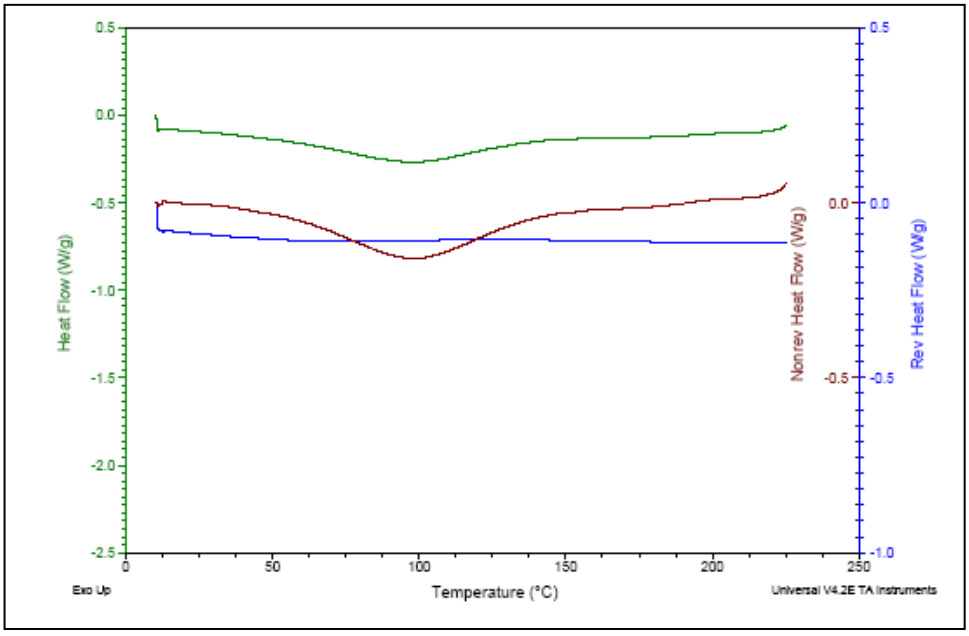

Figure 6.33. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine HCl, concentration 4% w/w, sample weight 4.9 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

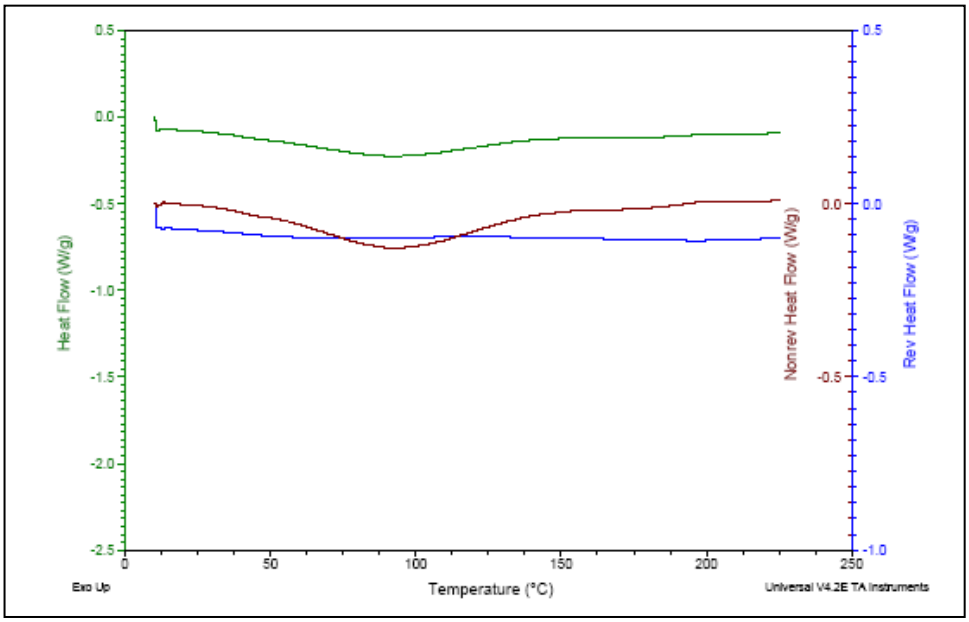

Figure 6.34. Temperature modulated thermogram of dried Xanthan Gum gel with Orphenadrine HCl, concentration 6% w/w, sample weight 5.0 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

6.2.2.4. Influence of sample encapsulation type on the thermal behaviour of samples:

The thermal behaviour of hydrophilic polymers could be influenced by the type of encapsulation used in sample preparation. Highly sealed pans in the form of hermetically sealed ones prevent the loss of moisture outwards from the internal environment within the pan. This could in turn have a clear influence on the thermal behaviour of the studied material. In all the thermal analysis studies carried out in this work, normal Aluminium crimped pans were used for sample encapsulation, thus allowing, to a certain extent, moisture loss from the pan, which is in line with the main pattern used in these studies, i.e. minimising the influence of water on the thermal behaviour of the samples. In order to investigate

any potential effect caused by the moisture content of the powders, if not allowed to escape from the internal pan environment, thermal investigation was carried out on the physical mixtures containing the polymer and either of the two drugs. A method identical to that used with the crimped Aluminium pans was used with hermetically sealed pans. Significantly different thermal behaviours were noted for both powder physical mixtures in comparison to their behaviour using crimped Aluminium pans.

The thermal behaviour of Xanthan Gum and Orphenadrine Citrate physical powder mixture using hermetically sealed pans is presented in Figure 6.35. The thermogram exhibits two main endotherms, the first of which occurs in all heat flow signals and could be attributed to a melting process associated with the drug. However, the position of the peak is shifted downwards to 120°C in comparison to 136°C noted when using crimped Aluminium pan (Figure 6.24.).

The second broad endotherm occurs in both the total heat flow and non-reversing heat flow signals, indicating probably a dehydration process. No endotherm is noted at lower temperature values. The presence of such an endotherm in the thermogram obtained using Crimped Aluminium pans was attributed to the loss of moisture from Xanthan Gum.

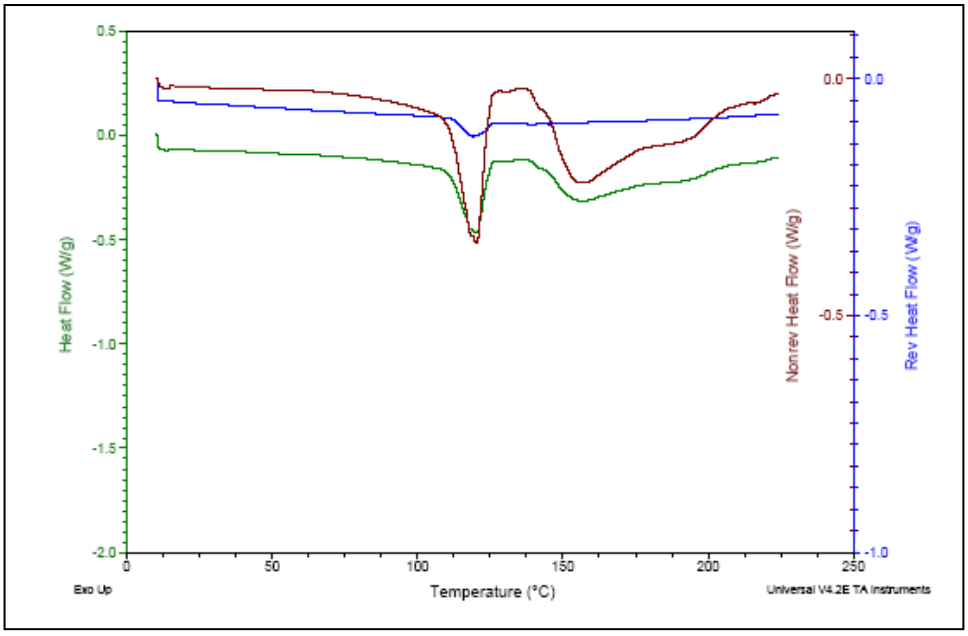

Figure 6.35. Temperature modulated thermogram of Xanthan Gum-Orphenadrine Citrate physical mixture in a hermetically sealed pan, sample weight 5.4 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

The change in the thermal behaviour of the physical powder mixture containing Xanthan Gum and the drug Orphenadrine HCl was much more apparent. The thermogram of such mixture using hermetically sealed pans is presented in Figure 6.36. It shows marked difference from the thermogram of the same sample using a crimped Aluminum pan (Figure 6.25.). The melting peak associated with the drug at 160°C, which should be clearly apparent mainly in the reversing heat flow signal is missing from the thermogram obtained using the hermetically sealed pan. Such behaviour could be attributed to the high aqueous solubility of the drug in comparison to the sparingly soluble Orphenadrine Citrate. The presence of moisture in the internal environment of the pan could have lead to the

dissolution of the drug, and subsequently to its interaction with Xanthan Gum. The presence of moisture within the pan is attributed mainly to the moisture content of Xanthan Gum, which had been previously determined to be 12.5% w/w (Chapter 3).

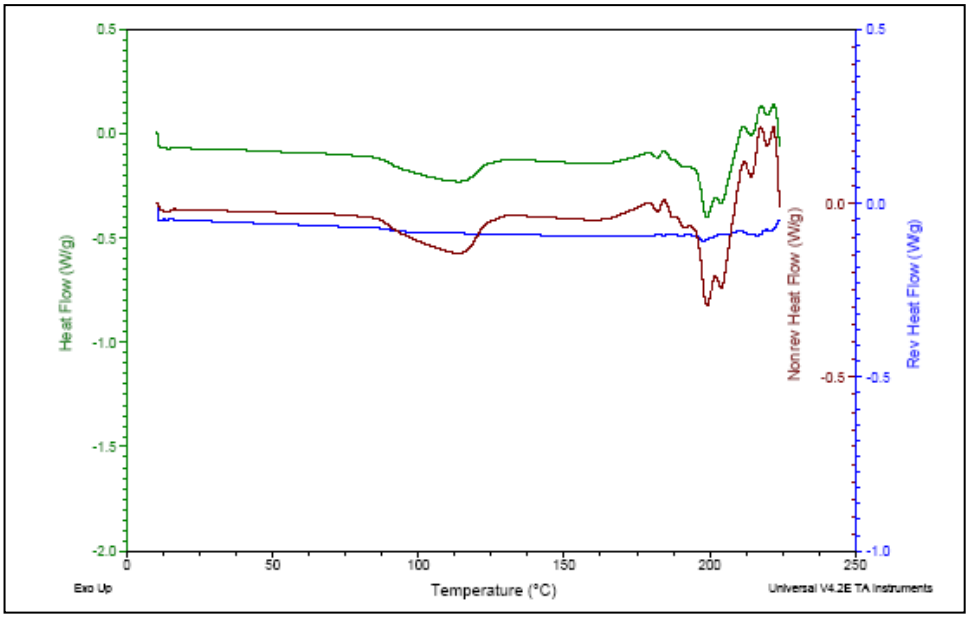

Figure 6.36. Temperature modulated thermogram of Xanthan Gum-Orphenadrine HCl physical mixture in a hermetically sealed pan, sample weight 5.4 mg, oscillation amplitude: 0.5 °C, oscillation period: 50 seconds.

6.3. General discussion and conclusions:

The results of the rheological investigations presented in this chapter clearly indicated a significant influence of the nature of the formulation used in tablet production on the properties of the gel layer produced on the outer surface of such tablets upon hydration. Changing the type of the model drug incorporated into the formulation had a profound influence on

the rheological behaviour of the gels produced using the formulation. Incorporating the drug Orphenadrine HCl had the most obvious effect on the structural integrity of the produced gels. Moreover, the influence exerted by the drug became more profound with increased concentration. Such results give clear insight into the swelling patterns associated with Xanthan Gum tablets containing this drug (Chapter 5), in which enhanced erosion was marked in the early hydration stages of the tablets due to the high concentration of the soluble drug in the gel layer region. The enhanced gel integrity at lower concentrations could also explain the enhanced swelling ability of the tablets with continuous hydration due to progressive drug out flux from the matrix.

As for the drug Orphenadrine Citrate, the results of the rheological studies indicated a rather enhanced structural integrity of Xanthan Gum gels in the presence of this drug. However, the calorimetric investigations conducted on all gels, indicated that both cationic model drugs exhibited clear interaction with the anionic Xanthan Gum upon hydration, and this explains the decreased swelling ability of Xanthan Gum gels containing either of the two drugs.

With regards to the major differences in the rheological properties of the gels produced using either of the two drugs, factors other than the potential interaction between drug and polymer may have contributed to this behaviour. The difference in drug solubility may have a two fold influence on the produced gel layer. Initially, the amount of drug

immediately available for interacting with the polymer would be greatly enhanced in the case of the more soluble drug Orphenadrine HCl . Secondly, the influence of the acidic part of the drug molecule, i.e. the Hydrochloride and the Citrate moieties, on the pH of the hydration medium available in the internal microenvironment of the gel layer may be greatly enhanced by the increased solubility of the drug in the case of Orphenadrine HCl. This in turn could have an added inhibitory effect on the ionisation of the acidic pyruvate and acetate moieties on the side chains of the Xanthan Gum molecules, thus, further diminishing the swelling ability of the polymer.

It becomes clear that changing the nature of the formulation used in the production of Xanthan Gum hydrophilic matrix tablets, more precisely, the nature of the drug incorporated into the formulation, has a profound effect on the properties of the gel layer formed on the outer surface of the tablets.

CHAPTER SEVEN

7. Dissolution Studies

7.1. Introduction:

The results obtained form the various in-vitro investigations conducted on the Xanthan Gum hydrophilic matrix tablets used in this study indicated that changing the face curvature and overall porosity of round and elongated tablets exerted a significant influence on the physical properties of the tablets and on the hydration behaviour of such tablets. Moreover, incorporation of either of the two drugs Orphenadrine Citrate or Orphenadrine HCl had a clear and differing influence on tablet behaviour and properties.

It was thus the objective of this part of this study to investigate the influence of such changes on the ultimate process of tablet dissolution. Moreover, it was another objective to investigate the influence of some of the hydration patterns noted during tablet hydration studies on drug release, namely the occurrence of cracks within the structure of the tablets and its possible influence on drug release.

Another objective of this part of the work was to explore the potential of statistical methods in the comparison of tablet dissolution profiles, and in the clarification of the effects associated with different variables and possible interactions between such effects.

In a manner similar to that used in the investigation of the hydration patterns of the tablets, the results of tablet dissolution studies are reported in the form of percentage drug and polymer dissolved. This was done in order to elucidate the extent of drug and polymer dissolution in releation to their initial amounts in the dry tablets. This would give further indication on the extent of tablet hydration and how this is influenced by the change in tablet porosity and geometry, leading to the change in the internal structure of the different tablets and their surface area to volume ratio. This would give a more comparable picture into the overall hydration and subsequent dissolution patterns of tablets with different curvatures than absolute drug release amounts. Moreover, the use of percentage drug release values is a required normalisation process if tablets containing different amount of drug in their dry state are to be compared.

7.2. Results and Discussion:

7.2.1. Determination of drug and polymer absorbance contributions:

Initial investigative studies indicated that within each tablet type, two entities contribute to the total absorbance recorded during tablet dissolution studies, namely the incorporated drug and the hydrophilic

polymer Xanthan Gum. This pattern was utilised to make simultaneous determination of drug and polymer absorbance contributions. Two wavelengths were chosen to measure dissolution sample absorbance during tablet dissolution studies, namely 264 nm and 244 nm. At 264 nm both drugs showed maximum absorbance in accordance with previous literature (Moffat et al 2004). At 244 nm the drugs absorbed light sufficiently to be able to define a clear relationship between concentration and absorbance also. At both wavelengths Xanthan Gum showed significant light absorption as a function of concentration of the polymer in the solution. The absorbance values for all entities at the wavelength of 244 nm were clearly different from those measured at the wavelength of 264 nm.

Calibration curves were constructed for both drugs and for Xanthan Gum in distilled deaerated water at both wavelengths, covering the complete concentration ranges expected during the tablet dissolution investigations conducted in this study. The drug Orphenadrine is reported to exhibit no alkaline shift in its UV absorbance (Moffat et al 2004), and this was also apparent from the high linearity of the calibration curves of both drugs at both wavelengths of 264 nm and 244 nm. The linear regression equations obtained for the two drugs and polymer are reported in Table 7.1., and the graphical representations of the calibration curves are reported in the appendix.

As a consequence of the presence of two absorbing entities within the dissolution medium, the total recorded absorbance at each of the two wavelengths is composed of two parts associated with the contributions of the dissolved fraction of the drug that is incorporated into the tablet and with the dissolved Xanthan Gum which is in a colloidal system in the dissolution medium (Equations 7.1. and 7.2.)

Material	Wavelength (nm)	Calibration equation	R^2
Orphenadrine Citrate	264	y = 0.0013x + 0.0039	0.9999
	244	y = 0.0006x + 0.0040	0.9996
Orphenadrine HCl	264	y = 0.0020x + 0.0051	0.9999
	244	y = 0.0009x + 0.0017	0.9999
Xanthan Gum	264	y = 0.0007x + 0.0074	0.9995
	244	y = 0.0009x + 0.0097	0.9992

Table 7.1. Calibration equations for drugs and polymer, where y is the absorbance of the material at the specified wavelength, and x is the concentration of the material.

$$Abs_{\text{-total-264nm}} = Abs_{\text{-drug-264nm}} + Abs_{\text{-polymer-264nm}} \qquad \textbf{Equation 7.1.}$$

where $Abs_{\text{-total-264nm}}$ is the total measured absorbance at λ = 264 nm, $Abs_{\text{-drug-264nm}}$ is the absorbance attributed to either of the two drugs at λ = 264 nm, and $Abs_{\text{-polymer-264nm}}$ is the absorbance attributed to Xanthan Gum at λ = 264 nm.

$Abs_{\text{-total-244nm}} = Abs_{\text{-drug-244nm}} + Abs_{\text{-polymer-244nm}}$ **Equation 7.2.**

where $Abs_{\text{-total-244nm}}$ is the total measured absorbance at λ = 244 nm, $Abs_{\text{-drug-244nm}}$ is the absorbance attributed to either of the two drugs at λ = 244 nm, and $Abs_{\text{-polymer-244nm}}$ is the absorbance attributed to Xanthan Gum at λ = 244 nm.

The above equations consist of a total of four different unknown values. The first two are the absorbance contributions of either of the two drugs at 264 nm and at 244 nm. The other two are the absorbance contributions of Xanthan Gum at 264 nm and at 244 nm.

The absorbance as a function of concentration was determined for each drug and Xanthan Gum individually at both wavelengths. Linear regression equations were obtained from each set of absorbance data representing the relationship between the absorbance of every absorbing entity at the two wavelengths of 264 nm and 244 nm (Equations 7.3. to 7.5.).

$Abs_{\text{-Xanthan-244nm}} = 1.1822*Abs_{\text{-Xanthan-264nm}} + 0.0009$ **Equation 7.3.**
($R^2 = 0.9996$)

$Abs_{\text{-Citrate-244nm}} = 0.4679*Abs_{\text{-Citrate-264nm}} + 0.0023$ **Equation 7.4.**
($R^2 = 0.9996$)

$Abs_{\text{-HCl-244nm}} = 0.4672*Abs_{\text{-HCl-264nm}} - 0.0007$ **Equation 7.5.**
($R^2 = 0.9998$)

The determination of the previously mentioned four unknown absorbance values was possible using four of the developed linear equations, namely equations 7.1., 7.2., 7.3., and either of the two equations 7.4., and 7.5. depending on the type of drug incorporated into the studied tablets.

The solution of the required equations to derive the values for the absorbance were obtained using the solver “add-in” of the software Microsoft Excel® . This programme was used to solve the four linear equations simultaneously to obtain the absorbance values associated with either of the two drugs and Xanthan Gum at the two wavelengths. As mentioned in Chapter 2, each sample was measured for absorbance at both wavelengths. Thus, each pair of absorbance readings were analysed together for their drug and polymer components.

7.2.2. Dissolution studies for round tablets:

The drug and polymer dissolution profiles for round Xanthan Gum tablets containing either Orphenadrine Citrate or Orphenadrine HCl with an overall porosity of 12.5% are presented in Figures 7.1. to 7.4. The dissolution profiles of tablets produced at the three different degrees of tablet overall porosity were rather super-imposable. Thus, the dissolution profiles of tablets with the two other degrees of tablet overall porosity are presented in the appendix to ensure clarity.

In terms of drug dissolution, it is clear that the process of drug release from tablets containing the drug Orphenadrine Citrate (Figure 7.1.) follows a rather steady rate throughout the dissolution process after an initial fast release pattern “burst” within the first 60 minutes. Such pattern is more evident in flat tablets and tablets with the lower degree of face curvature ratio (R/D) of 0.5. Tablets with the two higher degrees of face curvature ratio of 1 and 1.43 exhibited steady drug release behaviour throughout the dissolution process without initial burst. A clear reduction in the percentage of drug released could be observed with the increase in tablet face curvature ratio (R/D). This could be attributed mainly to the increase in tablet volume with the increase in tablet face curvature.

Tablets containing the drug Orphenadrine HCl (Figure 7.3.) exhibited a rather different dissolution behaviour in terms of drug release. A more rapid release of the drug was evident in the initial stages of drug release as compared to tablets containing the drug Orphenadrine Citreate. Such enhanced drug release was more noticeable in flat tablets, and decreased with the increase in tablet face curvature ratio. With progressive hydration and thus dissolution, the process of drug release seemed to slow down significantly, as noted by the clear flattening of the drug release profiles. This behaviour could be attributed to multiple reasons. Initially the release of the free dissolved drug from within the tablet reduces the osmotic pressure which could be considered as the main driving force in the release of the free soluble cationic drug Orphenadrine HCl when it is liberated from any ionic interaction with the

anionic Xanthan Gum. Another important feature associated with such tablets is their hydration and swelling patterns. With progressive hydration, a uniform gel layer formed on the surface of the tablets in place of the highly irregular gel layer noted within the initial hydration phase. This was identified by the enhanced swelling ability of such tablets during the later stages of hydration (Chapter 5). This process in turn increased the thickness of the gel layer and thus reduced the rate of further hydration and any subsequent release of dissolved free drug molecules.

One feature associated with the patterns of drug release from round tablets containing the drug Orphenadrine HCl could be noted from the drug release profiles associated with tablets with face curvature degrees of 0.5 and 1. It can be seen from Figure 7.3., both release profiles are rather super-imposable. This finding could be attributed to the process of crack formation within such tablets during the initial phases of hydration (Chapter 5). This behaviour was more noticeable within tablets with the two higher degrees of face curvature ratio of 1 and 1.43. Such crack formation could enhance the process of water penetration into the dosage form and the subsequent tablet hydration and drug release by increasing the surface area in contact with the surrounding hydration medium. This pattern is clearly obvious in the enhanced drug release process from tablets with a face curvature ratio of 1. Tablets with a face curvature ratio of 1.43 exhibited clear crack formation. However, the large volume of such tablets and the subsequent need for longer time for thorough tablet

hydration may have reduced the effect that such pattern of crack formation has on drug dissolution.

More insight into the dissolution behaviour of the different round tablets could be noted from the polymer dissolution profiles associated with them (Figures 7.2. and 7.4.). Polymer dissolution from tablets containing the drug Orphenadrine Citrate (Figure 7.2.) was slow within the initial dissolution phase. With progressive hydration an enhancement of polymer dissolution could be noted from all Orphenadrine Citrate containing tablets, the percentage of which decreased with the increase in tablet face curvature ratio (R/D), in a manner similar to that noted with drug release. Such enhancement of polymer dissolution could be attributed to the polymer erosion process, in which polymer chains located on the surface of the gel layer are continuously hydrated and diluted until they detach from the surface and dissolve within the surrounding dissolution medium.

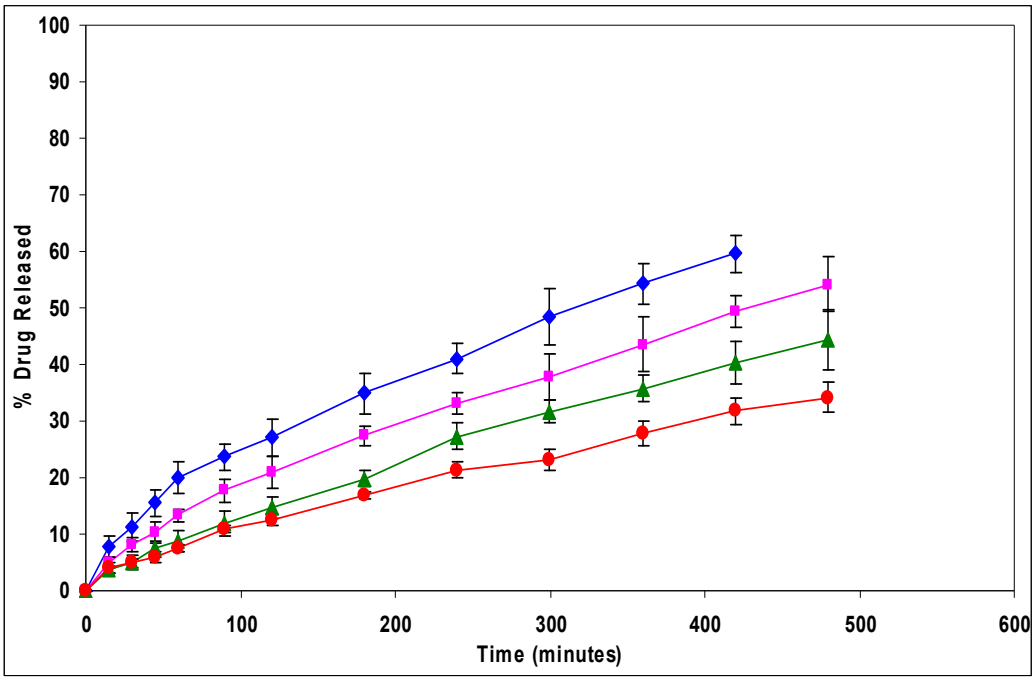

Figure 7.1. Percentage drug released from round Xanthan Gum tablets with Orphenadrine Citrate, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

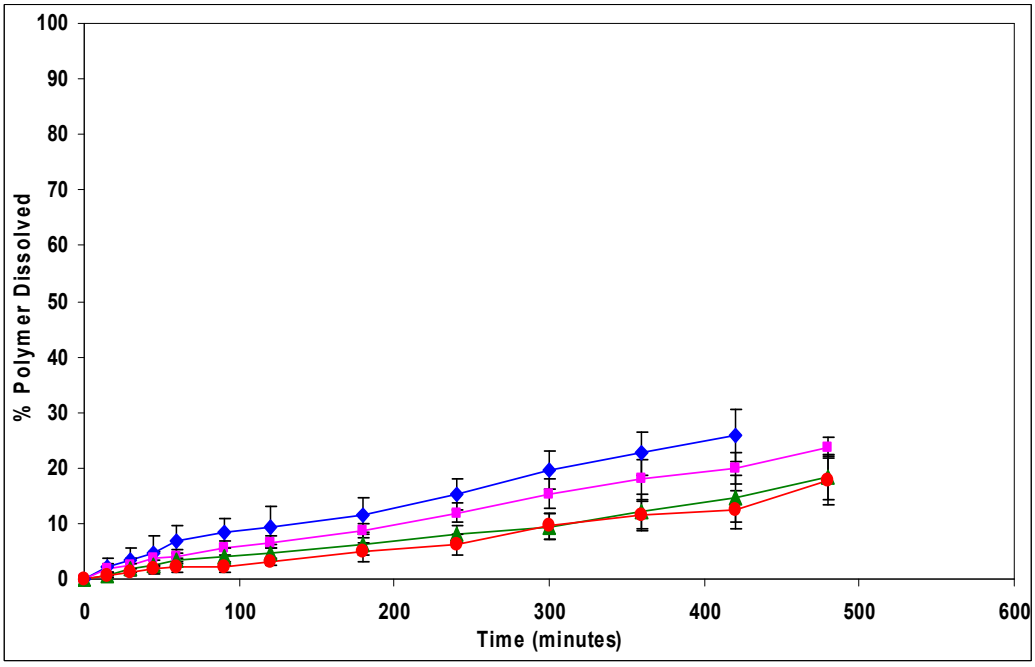

Figure 7.2. Percentage polymer dissolved from round Xanthan Gum tablets with Orphenadrine Citrate, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

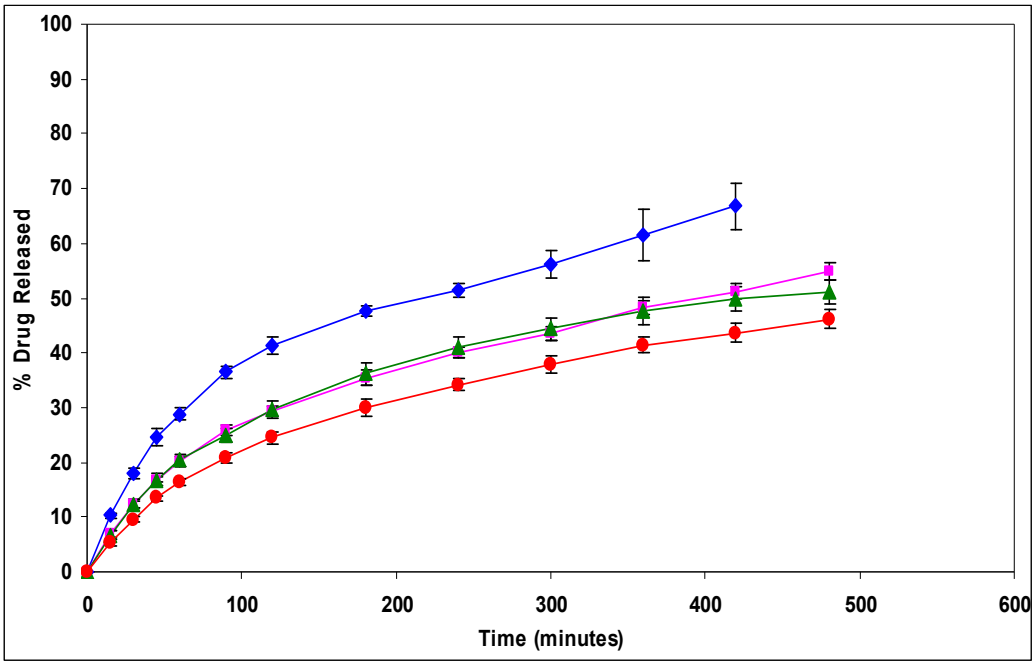

Figure 7.3. Percentage drug release from round Xanthan Gum tablets with Orphenadrine HCl, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

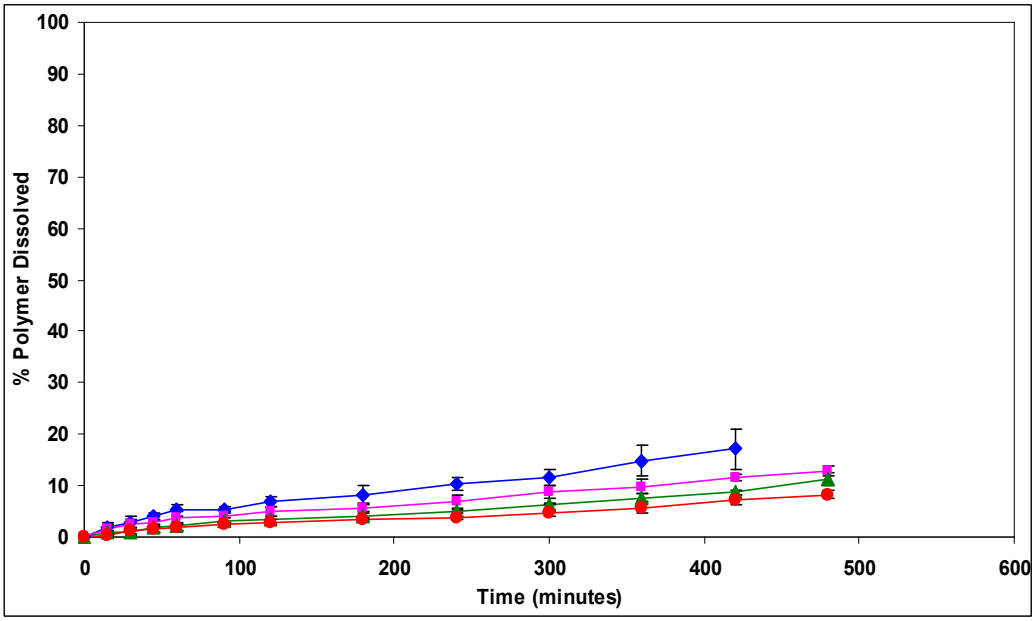

Figure 7.4. Percentage polymer dissolved from round Xanthan Gum tablets with Orphenadrine HCl, porosity 12.5%. -♦-(R/D= 0), -■-(R/D=0.5), -▲-(R/D=1), -●-(R/D=1.43), (n=6).

The pattern of polymer dissolution from Orphenadrine Citrate containing tablets could give more insight into the drug release patterns exhibited with such tablets. The process of polymer erosion and subsequent dissolution counteracts the retarding effect on drug release exhibited by the progressive formation of the gel layer on the surface of the tablet. Polymer erosion leads to the reduction in the thickness of the gel layer and thus reduces the pathway needed for water ingress and drug release. Moreover, polymer erosion could lead to the release of drug molecules together with the eroding polymer chains. Thus, for tablets used in this study, the enhanced polymer erosion and subsequent dissolution during the latter phases of tablet dissolution would have compensated for any reduction in drug release rate due to the thickening of the gel layer, giving rise to a steady rate or a zero order drug release process.

As for tablets containing the drug Orphenadrine HCl (Figure 7.4.), a slower process of polymer dissolution could be noted with such tablets. Apart from flat tablets, which exhibited some degree of enhanced polymer dissolution with progressive tablet dissolution, minimal increase in the percentage of polymer dissolved was noted with the other tablets. This behaviour further confirms the reduction of drug release from such tablet with progressive tablet dissolution.

During the latter stages of tablet dissolution, some of the flat tablet batches with lower weights floated within the dissolution vessels and

started hitting the paddle. Thus the samples withdrawn from such vessels were not used in further analysis, as indicated by their shorter dissolution profiles.

7.2.3. Statistical comparison of the dissolution parameters of round tablets:

A combined statistical approach was used for the comparison of the dissolution profiles of round tablets. In a manner similar to that employed in the comparison of the various swelling profiles of the tablets (Chapter 5), a combination of analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA) was used to make a thorough comparison between the various dissolution profiles. A comprehensive statistical comparison was conducted on the dissolution profiles, without the previously mentioned segments during which some of the tablets were hitting the paddles. Initially, MANOVA was employed to compare the complete dissolution patterns under investigation. Then, multiple ANOVA investigations were conducted at 60, 180 and 360 minutes. This was done to give more insight into the differences between the dissolution profiles of the various tablets, and compare any possible variations in such differences during the progressive phases of tablet dissolution.

7.2.3.1. Round Xanthan Gum tablets with Orphenadrine Citrate:

The results of the MANOVA investigation of drug and polymer dissolution profiles from round Xanthan Gum tablets with Orphenadrine Citrate are presented in Table 7.2. In terms of drug release it could be noted that both variables associated with the dosage form, i.e. tablet face curvature ratio and tablet overall porosity have a significant influence on the process of drug release from such tablets, and this is indicated by the significance p-values associated with these variables which are less than 0.001, i.e. lower that the significance threshold of 0.05. More importantly, it could be noted that the interaction between the two investigated factors is significant indicating a high dependence of the influence of either variable on the change in the value of the other.

A similar pattern could be noted for the process of polymer dissolution where both tablet face curvature ratio and tablet overall porosity seem to have a significant influence on polymer dissolution with significance p-values of less than 0.001 and 0.011, respectively. However, no significant interaction could be noted between the two variables, as the interaction product has a p-value of 0.128 which is considerably higher than the threshold of 0.05. Thus, there is clear indication that the influence on either of the two variables on polymer dissolution is completely independent from the other.

Dissolving entity	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Drug	Porosity	1.185	2.963	20.000	100.000	< 0.001
	Curvature	18.553	30.716	30.000	149.000	< 0.001
	Porosity*Curvature	2.980	2.450	60.000	296.000	< 0.001
Polymer	Porosity	0.820	2.050	20.000	100.000	0.011
	Curvature	4.771	7.899	30.000	149.000	< 0.001
	Porosity*Curvature	1.506	1.239	60.000	296.000	0.128

Table 7.2. MANOVA results for the dissolution profiles of round Xanthan Gum tablets with Orphenadrine Citrate.

More insight into the differences between the multiple drug and polymer dissolution profiles associated with the different Orphenadrine Citrate containing tablets could be noted from the results of the two-way ANOVA investigations conducted on them. In terms of drug release (Table 7.3.), certain trends can be noted. The influence of tablet face curvature on the process of drug release seems to be significant throughout the dissolution process, and this can be noted by the p-values associated with this variable which are consistently less than 0.001 at the three time points investigated. Tablet overall porosity seems to have a significant influence on drug release only at the initial time point of 60 minutes, indicated by with a p-value of less than 0.001. A significant interaction between the two variables can be noted at the first two time points of 60 and 180 minutes.

A consistently significant influence on polymer dissolution from these tablets was associated with the degree of tablet face curvature (Table 7.4.), and this is mirrored by the p-values associated with this variable

which are consistently less than 0.001 at all three time points. The influence associated with tablet overall porosity seems to be significant at the initial time points only with a p-value of 0.009 and 0.025 at 60 and 180 minutes, respectively. However, no significance is noted with this variable at the later time point of 360 minutes ($p = 0.709$). The interaction between the two variables also seems to be of significance during the initial dissolution phase with a p value of 0.039 at 60 minutes. No significance is associated with such interaction at the two later time points.

The two-way ANOVA investigations were followed by post hoc analysis using the Sheffé test to identify the differences between the various degrees of each of the two studied variables. When a significant interaction was noted between the two variable, different one-way ANOVA investigations were carried out at each of the three levels of tablet overall porosity of 12.5%, 15%, and 17.5%, followed by post hoc analysis using the Sheffé test to investigate the nature and extent of any difference between different degrees of tablet face curvature at every porosity value. The results of the Sheffé analysis (reported in the appendix) revealed some trends in the effects associated with the two variables; a progressive decrease in drug and polymer dissolution was noted with the increase in tablet face curvature, and the dissolution ability of flat tablets was considerably higher than that of the other tablets. Furthermore, small and inconsistent differences were noted between tablets produced at the three different values of overall porosity. Moreover, tablet overall porosity had a certain degree of influence on the

differences between the drug release profiles of Orphenadrine Citrate containing tablets with the four different degrees of face curvature. However, such differences, although significant in certain cases, were of small magnitude and this has to be taken into account during the interpretation of the results.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	16.902	< 0.001
	Curvature	3	131.841	< 0.001
	Porosity*Curvature	6	7.502	< 0.001
180	Porosity	2	1.315	0.276
	Curvature	3	180.692	< 0.001
	Porosity*Curvature	6	4.525	0.001
360	Porosity	2	2.862	0.065
	Curvature	3	180.804	< 0.001
	Porosity*Curvature	6	0.716	0.638

Table 7.3. Two -way ANOVA results for the drug dissolution profiles of round Xanthan Gum tablets with Orphenadrine Citrate.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	5.152	0.009
	Curvature	3	12.225	< 0.001
	Porosity*Curvature	6	2.395	0.039
180	Porosity	2	3.935	0.025
	Curvature	3	36.762	< 0.001
	Porosity*Curvature	6	1.766	0.122
360	Porosity	2	0.346	0.709
	Curvature	3	71.256	< 0.001
	Porosity*Curvature	6	1.392	0.233

Table 7.4. Two -way ANOVA results for the polymer dissolution profiles of round Xanthan Gum tablets with Orphenadrine Citrate.

7.2.3.2. Round Xanthan Gum tablets with Orphenadrine HCl:

The results of the MANOVA investigation of the dissolution profiles of round Xanthan Gum tablets with Orphenadrine HCl are listed in Table 7.5. A similar pattern could be noted with both drug and polymer dissolution, as both studied variables of tablet face curvature and tablet overall porosity seem to have a significant influence on the process of tablet dissolution as noted by the p values associated with them. Also, a significant interaction can be noted between the influence of both variables on the process of drug and polymer dissolution.

Dissolving entity	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Drug	Porosity	2.082	5.204	20.000	100.000	< 0.001
	Curvature	42.045	69.608	30.000	149.000	< 0.001
	Porosity*Curvature	1.924	1.582	60.000	296.000	0.007
Polymer	Porosity	7.134	17.836	20.000	100.000	< 0.001
	Curvature	18.164	30.072	30.000	149.000	< 0.001
	Porosity*Curvature	2.070	1.702	60.000	296.000	0.002

Table 7.5. MANOVA results for the dissolution profiles of round Xanthan Gum tablets with Orphenadrine HCl.

Investigating the progressive tablet dissolution stages using two-way ANOVA (Tables 7.6. and 7.7.) revealed that for both drug and polymer dissolution, the degree of tablet face curvature plays a significant role throughout the dissolution process. A rather similar influence could be noted associated with tablet porosity with one exception being the lack of significance associated with this factor on drug dissolution at 360 minutes. As for the interaction between the influences of tablet face

curvature and tablet overall porosity, an opposing picture could be seen with drug and polymer dissolution, where a significant interaction was apparent at the two initial time points of 60 and 180 minutes in the case of drug dissolution, on the other hand a significant interaction was only noted at the latter time point of 360 minutes in the case of polymer dissolution.

Multiple one-way ANOVA in the presence of significant interaction between the two main variables, and Post hoc analysis using the Sheffé test were conducted to allocate the differences between the different tablets. The results of such analysis (reported in the appendix) show a pattern where tablet dissolution decreases with the increase in tablet face curvature, and a smaller influence associated with tablet overall porosity.

It can be noted from the multiple statistical comparisons conducted on the different tablets that the magnitude of the F values associated with the studied variables in tablets containing the drug Orphenadrine HCl are consistently higher than those associated with the same variables in tablets containing the drug Orphenadrine Citrate. Such a finding could indicate that the magnitude or clarity of the differences between the different degrees of the studied variables is higher in tablets containing the drug Orphenadrine HCl. This pattern could be related to the different hydration and subsequent dissolution patterns associated with the tablets produced using the two different drugs.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	28.974	< 0.001
	Curvature	3	524.550	< 0.001
	Porosity*Curvature	6	7.816	< 0.001
180	Porosity	2	22.111	< 0.001
	Curvature	3	592.605	< 0.001
	Porosity*Curvature	6	5.509	< 0.001
360	Porosity	2	2.518	0.089
	Curvature	3	319.149	< 0.001
	Porosity*Curvature	6	1.395	0.232

Table 7.6. Two -way ANOVA results for the drug dissolution profiles of round Xanthan Gum tablets with Orphenadrine HCl.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	55.745	< 0.001
	Curvature	3	78.469	< 0.001
	Porosity*Curvature	6	1.281	0.280
180	Porosity	2	70.502	< 0.001
	Curvature	3	121.067	< 0.001
	Porosity*Curvature	6	1.829	0.109
360	Porosity	2	27.013	< 0.001
	Curvature	3	139.365	< 0.001
	Porosity*Curvature	6	2.827	0.017

Table 7.7. Two -way ANOVA results for the Polymer dissolution profiles of round Xanthan Gum tablets with Orphenadrine HCl.

7.2.4. Dissolution studies of elongated tablets:

Drug and polymer dissolution profiles for elongated Xanthan Gum tablets containing both Orphenadrine Citrate and Orphenadrine HCl are presented in Figures 7.5 to 7.8. A drug-type dependent dissolution behaviour can bee seen in terms of drug release. Tablets containing the

drug Orphenadrine Citrate exhibit a steady drug release process (Figure 7.5.), and this could be justified by the enhanced polymer dissolution during the later stages of the dissolution process (Figure 7.6) in a manner similar to that observed with round tablets. As for tablets containing the drug Orphenadrine HCl, a sharp reduction in drug release could be observed during the latter stages of tablet dissolution (Figure 7.7.). This was coupled with the clear visible formation of a gel layer and disappearance of cracks from within the tablet structure. A certain degree of polymer dissolution could be observed in these tablets especially flat ones (Figure 7.8.).

One factor that may have an additional influence on the dissolution characteristics of round and elongated Xanthan Gum tablets containing the two different drugs, i.e. Orphenadrine Citrate and Orphenadrine HCl, is the potential process of ionic interaction between the polymer and the two drugs. The rate of ionic interaction and complex formation between the drug and polymer, and the subsequent dissolution of such complex leading to drug and polymer release from within the matrix system, can be highly influenced by the solubility and dissolution properties of the drug particles (Lapidus and Lordi 1968), and of the complex upon formation (Takka 2003). Thus, a complex process governs the structural and physico-chemical features of the hydrated tablet, leading to variations in the properties of the gel layer as noted previously in Chapters 5 and 6. This in turn would lead to variations in the diffusion and erosion patterns within the tablet.

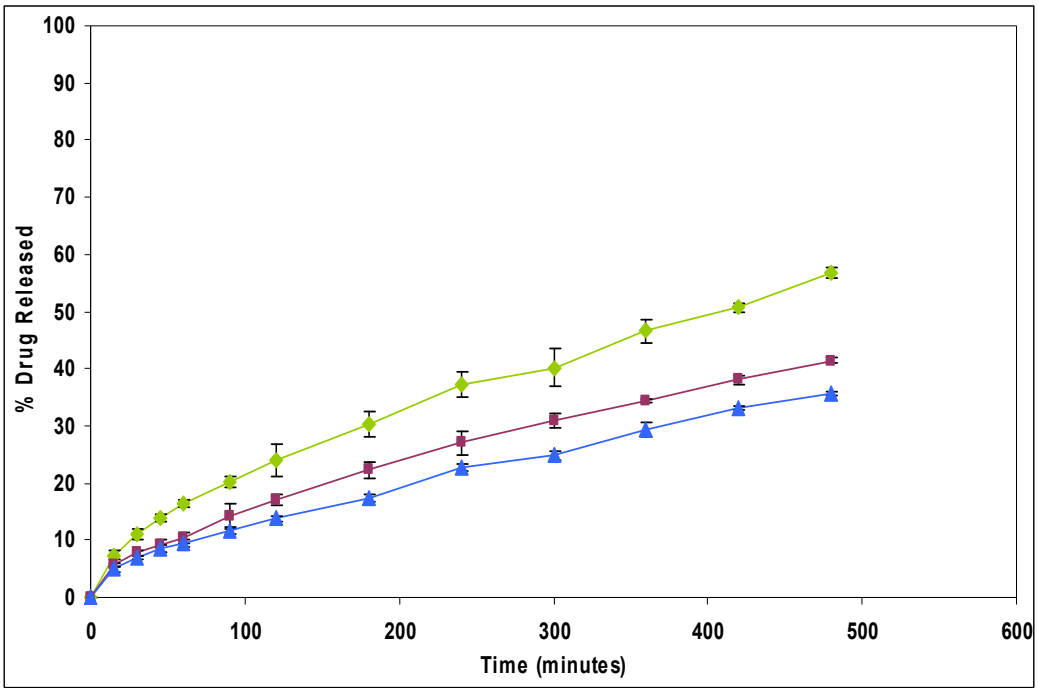

Figure 7.5. Percentage drug released from elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%. -♦-(curvature height 0 mm), -■-(curvature height 1mm), -▲-(curvature height 2 mm), (n=3).

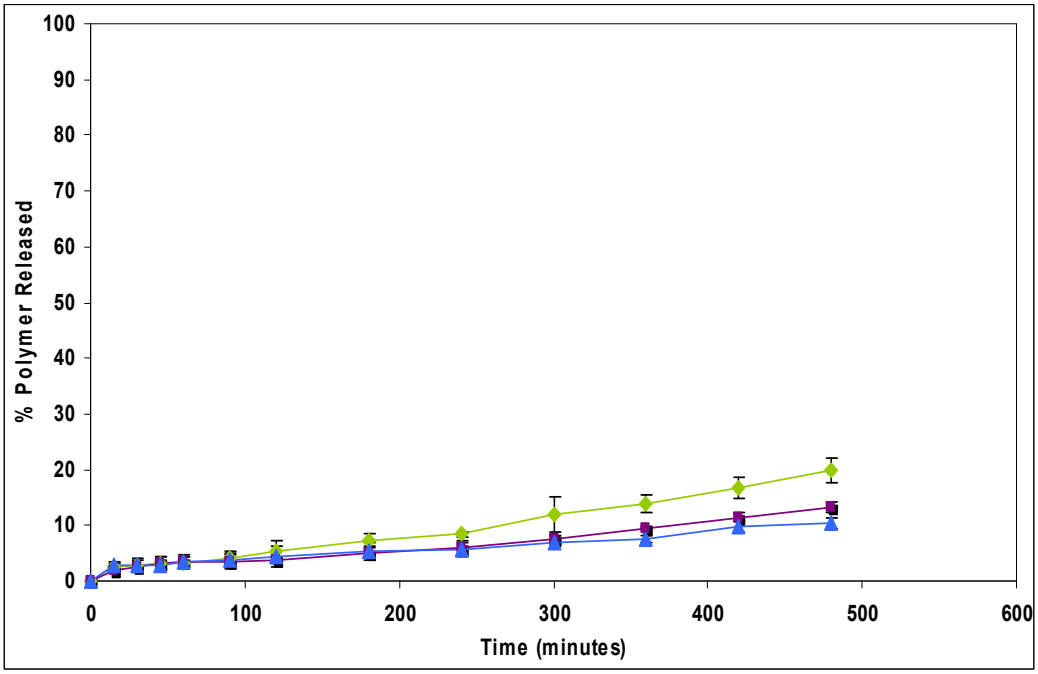

Figure 7.6. Percentage polymer dissolved from elongated Xanthan Gum tablets with Orphenadrine Citrate, porosity 15.0%. -♦-(curvature height 0 mm), -■-(curvature height 1mm), -▲-(curvature height 2 mm), (n=3).

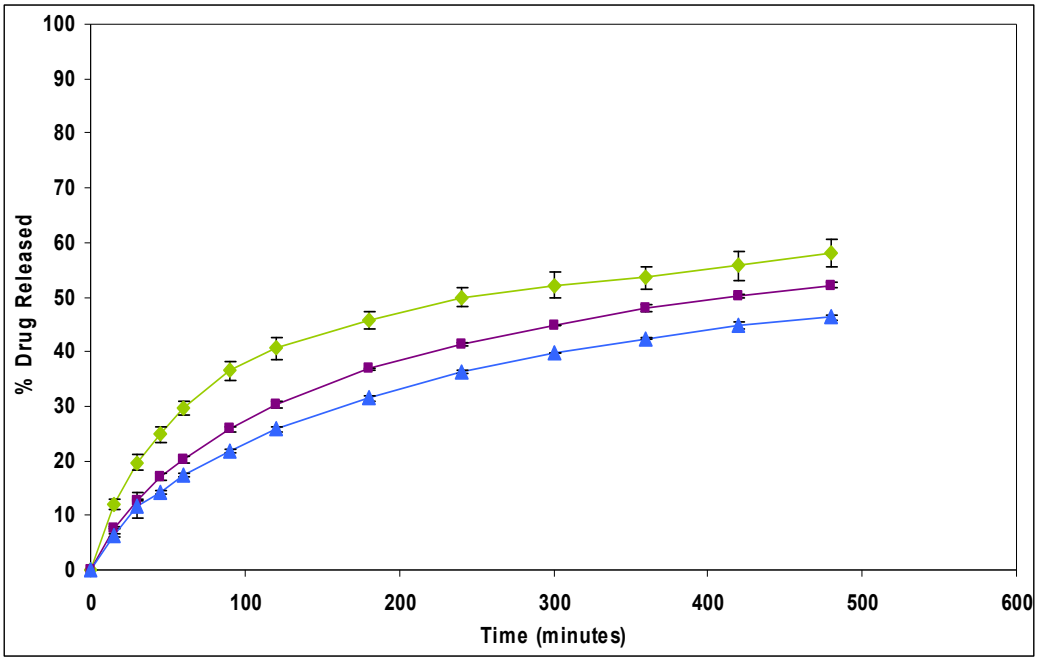

Figure 7.7. Percentage drug released from elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%. -♦-(curvature height 0 mm), -■-(curvature height 1mm), -▲-(curvature height 2 mm), (n=3).

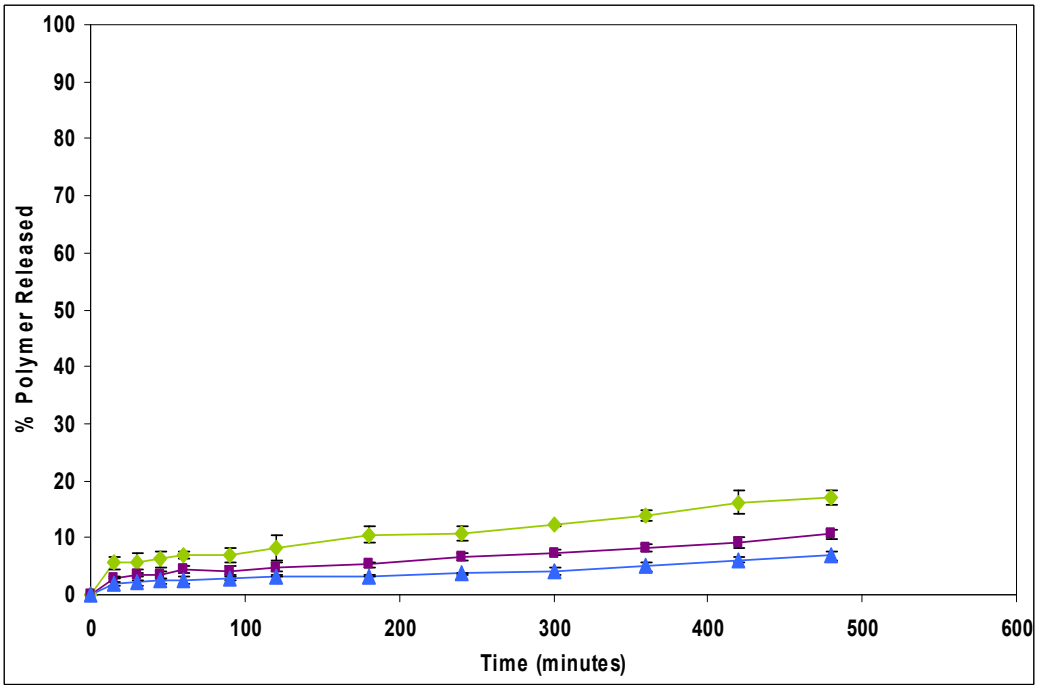

Figure 7.8. Percentage polymer dissolved from elongated Xanthan Gum tablets with Orphenadrine HCl, porosity 15.0%. -♦-(curvature height 0 mm), -■-(curvature height 1mm), -▲-(curvature height 2 mm), (n=3).

7.2.5. Statistical comparison of the dissolution profiles of elongated tablets:

7.2.5.1. Elongated Xanthan Gum tablets with Orphenadrine Citrate:

Statistical analysis was carried out to explore the influences of tablet variables in terms of face curvature and overall porosity on tablet dissolution characteristics. It can be seen from the results of the MANOVA investigations conducted on the drug and polymer dissolution profiles from elongated Xanthan Gum tablets containing the drug Orphenadrine Citrate (Table 7.8.) that the only factor to exert a significant influence on the overall drug and polymer dissolution process is the degree of tablet face curvature as indicated by the p values associated with this variable of less than 0.001 and 0.001 for drug and polymer dissolution, respectively. On the other hand, no significant influence can be noted due to the change in tablet overall porosity, as the p-values associated with this variable are higher than the threshold of 0.05. Moreover, no significant interaction can be noted between the two tablet variables.

Dissolving entity	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Drug	Porosity	4.567	1.827	20.000	16.000	0.113
	Curvature	98.869	39.547	20.000	16.000	< 0.001
	Porosity*Curvature	5.627	1.055	40.000	30.000	0.445
Polymer	Porosity	4.915	1.966	20.000	16.000	0.087
	Curvature	11.753	4.701	20.000	16.000	0.001
	Porosity*Curvature	6.966	1.306	40.000	30.000	0.225

Table 7.8. MANOVA results for the dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate.

Time dependent changes in the influences associated with both tablet variables were investigated using multiple two-way ANOVA. The results of these studies (Tables 7.9. and 7.10.) provide an image of a dissolution process in which tablet face curvature is the only variable significantly influencing the process of drug and polymer dissolution from within the tablet. This is indicated by the p values associated with this variable throughout the process of drug and polymer dissolution.

On the other hand, no significance is associated with the change in tablet overall porosity, or with the interaction between the two tablet variables “face curvature” and “overall porosity”. One exception is the initial phase of drug release at 60 minutes where the p-values associated with tablet overall porosity and the interaction between the two tablet variables are 0.001 and 0.013, respectively, and thus are lower than the threshold of 0.05. This indicates that tablet overall porosity may affect the initial process of drug release, but with subsequent hydration its influence becomes negligible.

The results of the Sheffé analysis conducted on these tablets (reported in the appendix) indicated that for drug release a consistent image was observed throughout the dissolution process in which a progressive decrease in drug dissolution was noted with the increase in tablet face curvature. The differences between tablets with the multiple degrees of face curvature in terms of polymer dissolution changed with the increase

in time. Small differences were observed between tablets with different overall porosities.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	10.018	0.001
	Curvature	2	145.284	< 0.001
	Porosity*Curvature	4	4.290	0.013
180	Porosity	2	1.352	0.284
	Curvature	2	106.956	< 0.001
	Porosity*Curvature	4	0.763	0.563
360	Porosity	2	0.232	0.795
	Curvature	2	235.389	< 0.001
	Porosity*Curvature	4	0.489	0.744

Table 7.9. Two -way ANOVA results for the drug dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	0.544	0.590
	Curvature	2	6.041	0.010
	Porosity*Curvature	4	2.052	0.130
180	Porosity	2	2.038	0.159
	Curvature	2	17.273	< 0.001
	Porosity*Curvature	4	1.542	0.233
360	Porosity	2	2.241	0.135
	Curvature	2	33.048	< 0.001
	Porosity*Curvature	4	1.868	0.160

Table 7.10. Two -way ANOVA results for the polymer dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine Citrate.

7.2.5.2. Elongated Xanthan Gum tablets with Orphenadrine HCl:

A rather different behaviour could be seen with elongated Xanthan Gum tablets containing the drug Orphenadrine HCl. The MANOVA investigation of the dissolution process associated with such tablets (Table 7.11.) indicated that the face curvature of the tablets significantly influences both drug and polymer dissolution, whereas, tablet overall porosity had a significant influence on polymer dissolution only. As for the interaction between the two variables, the results of the MANOVA investigation indicated that it is of significance for both drug and polymer dissolution processes.

Dissolving entity	Variable	Hotelling's Trace value	F	Hypothesis df	Error df	p
Drug	Porosity	4.665	1.866	20.000	16.000	0.105
	Curvature	295.467	118.187	20.000	16.000	< 0.001
	Porosity*Curvature	11.473	2.151	40.000	30.000	0.016
Polymer	Porosity	60.461	24.185	20.000	16.000	< 0.001
	Curvature	239.221	95.688	20.000	16.000	< 0.001
	Porosity*Curvature	11.793	2.211	40.000	30.000	0.013

Table 7.11. MANOVA results for the dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine HCl.

Time dependent changes in the significance characteristics of the influences associated with both "face curvature" and "overall porosity" are reported in the results of the two-way ANOVA investigations conducted for both drug and polymer dissolution (Table 7.12 and 7.13.). The results indicate that both variables have a significant influence on the process of

drug and polymer dissolution at the multiple time points, as indicated by the p-values associated with them. A time dependent significance was associated with the interaction between the two variables (see Table 7.13.). However, it could also be seen that the p-values associated with tablet face curvature are considerably lower than those associated with tablet overall porosity in the case of drug dissolution. It could thus be concluded that tablet face curvature is the main factor governing drug release.

The results of the post hoc Sheffé tests conducted on the dissolution profiles of these tablets (reported in the appendix), indicated a pattern in which drug dissolution progressively decreased with the increase in tablet face curvature, with rather minor influence associated with tablet overall porosity. In terms of polymer dissolution, increasing the degree of tablet face curvature led to a small decrease in the percentage of polymer dissolved with small variations between tablets with different overall porosity values.

An observation, similar to that noted with round tablets, could be made from the statistical comparison of elongated tablets, where the F-values associated with tablet variables in tablets containing the drug Orphenadrine HCl are consistently higher than those associated with the same variables in tablets containing the drug Orphenadrine Citrate.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	3.682	0.046
	Curvature	2	601.329	< 0.001
	Porosity*Curvature	4	0.886	0.492
180	Porosity	2	7.711	0.004
	Curvature	2	819.130	< 0.001
	Porosity*Curvature	4	3.938	0.018
360	Porosity	2	3.595	0.049
	Curvature	2	293.995	< 0.001
	Porosity*Curvature	4	2.219	0.108

Table 7.12. Two -way ANOVA results for the drug dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine HCl.

Dissolution time (min)	Variable	df	F	p
60	Porosity	2	22.390	< 0.001
	Curvature	2	43.217	< 0.001
	Porosity*Curvature	4	3.202	0.038
180	Porosity	2	35.371	< 0.001
	Curvature	2	101.919	< 0.001
	Porosity*Curvature	4	10.779	< 0.001
360	Porosity	2	29.471	< 0.001
	Curvature	2	128.238	< 0.001
	Porosity*Curvature	4	2.101	0.123

Table 7.13. Two -way ANOVA results for the polymer dissolution profiles of elongated Xanthan Gum tablets with Orphenadrine HCl.

7.3. General discussion and conclusions:

The results of this chapter clearly indicate the influence of tablet face curvature on the dissolution charactersictics of round and elongated hydrophilic matrix tablets based on Xanthan Gum. Both drug and polymer dissolution patterns were significantly infuenced by the change in tablet

face curvature. Moreover, the increase in tablet face curvature in tablets formulated using the drug Orphenadrine HCl, led to increase in the extent of crack formation within the tablets during their initial dissolution phases. This comes in accordance with similar results obtained from the swelling studies conducted on such tablets (Chapter 5). The influence of such behaviour on tablet dissolution characteristics was most evident in round tablets with a face curvature ratio (R/D) of 1, in which crack formation led to an enhanced drug release from the tablets.

In terms of Tablet overall porosity, a less evident influence was noted for this variable on tablet dissolution properties. This comes in accordance with similar results obtained with tablet swelling studies (Chapter 5).

Tablets formulated using the two different drugs, i.e. Orphenadrine Citrate and Orphenadrine HCl, exhibited different dissolution characteristics. Drug dissolution from tablets formulated using Orphenadrine Citrate followed a steady process. On the other hand, tablets containing the drug Orphenadrine HCl exhibited rapid drug release initially followed by a progressive decrease in the drug release process. Such difference could arise from the different physico-chemical natures of the drugs, in terms of their different solubility and their potential interaction with Xanthan Gum.

CHAPTER EIGHT

8. General conclusions and future work:

8.1. General conclusions:

Hydrophilic matrix tablets provide a therapeutically and economically convenient means for oral modified drug delivery. However, the mechanism of action of such dosage forms is comprised of a complex mixture of water penetration, tablet expansion and swelling leading to the formation of a gel layer that acts as the main regulator of further tablet hydration and dissolution. Furthermore, a review of the available literature, which was reported in Chapter 1, indicated that numerous factors could influence the action of such dosage forms. Moreover, significant interactions could exist between the influences associated with the different factors resulting in a complex process affecting the behaviour of such dosage forms. The shape (Ford et al 1987, Reynolds et al 2002) and formulation (Lapidus and Lordi 1968, Colombo et al 1995) properties of hydrophilic matrix tablets could have a significant influence on the in-vitro behaviour of such tablets. It is thus important to have a thorough knowledge of the influence of such factors or variables in order to facilitate the design and formulation of hydrophilic matrix tablets.

However, limited information is available about the influence of changing the degree of tablet face curvature on the behaviour of hydrophilic matrix tablets. It was thus the general aim of this research to investigate the influence of this factor and the concomitant change in tablet overall porosity and formulation nature on the properties and behaviour of hydrophilic matrix tablets.

Changing the parameters associated with the shape and structure of pharmaceutical tablets, in particular the face curvature of the tablets have a profound influence on the physical and structural properties of the tablets (Newton et al 2000a, Newton et al 2000b, Eiliazadeh et al 2003). The investigation of physical properties of the tablets used in this study (Chapter 4) indicated that changing the degree of face curvature of round and elongated hydrophilic matrix tablets based on Xanthan Gum had a significant effect on the tensile strength of such tablets. Changes in the internal structural properties of both round and elongated tablets in terms of overall tablet porosity also had a profound influence on the tensile strength of tablets. Moreover, it was apparent that the influences associated with both of the previously mentioned factors were significantly interacting in both round and elongated tablets, indicating that both factors have to be considered concurrently during the design of hydrophilic matrix tablets.

A clear change in the tensile strength values associated with round and elongated tablets, with the different face curvature and overall porosity

values, was noted upon changing the nature of the formulation used in tablet production. This was justified by the possible difference in the compaction properties of the different formulations as a result of the differences in the physico-chemical characteristics of the powders incorporated into them. These differences in powder properties were observed and reported in Chapter 3.

One of the main objectives of this work was to perform a comprehensive study of the hydration characteristics associated with round and elongated hydrophilic matrix tablets, and to investigate the influence of tablet face curvature, tablet overall porosity and formulation nature on the hydration and dimensional expansion of the tablets. The results of this investigation (Chapter 5) indicated that tablet face curvature acts as a significant factor on the dimensional swelling and expansion of round and elongated hydrophilic matrix tablets in the various tablet dimensions, where a decrease in tablet swelling ability was generally noted with the increase in tablet face curvature. This could be attributed to the change in the shape and volume of the tablets upon changing the degree of face curvature. This change, in addition to the resulting change in the internal structural nature of the tablets, would influence the nature and extent of tablet hydration and dimensional expansion.

A rather minor influence associated with tablet overall porosity on tablet swelling was noted. It could thus be concluded that although tablet overall porosity exerts a profound influence on the structural and physical

properties of tablets in their dry state, this variable exerts a much smaller influence on the hydration behaviour of the tablets.

One of the aims of this study was to investigate the influence of formulation nature on the behaviour of hydrophilic matrix tablets, more precisely, the influence of changing the solubility of the drug incorporated into the formulation. A particular case of hydrophilic matrix tablets was investigated in this study, in which there was a potential for an ionic interaction between the ionic and oppositely charged polymer and drug. This phenomenon could be regarded as a possible means to enhance the retardation of drug release from the matrix system. In this study the ionic entities with potential ionic interactions were the anionic Xanthan Gum and the two cationic drugs Orphenadrine Citrate and Orphenadrine HCl which differed in their solubility; the latter being more soluble. The results of the swelling studies (Chapter 5) indicated that incorporating either of the two drugs into Xanthan Gum tablets resulted in a significant decrease in the swelling ability of the tablets. Moreover, the effect seen upon incorporating Orphenadrine HCl was more profound than that of incorporating Orphenadrine Citrate.

The previously mentioned influence of drug incorporation on the swelling ability of round and elongated Xanthan Gum tablets was further clarified by the use of rheological and thermal studies (Chapter 6). The results of the thermal studies indicated that both cationic drugs seem to undergo a process of interaction with the anionic Xanthan Gum. This was evident

from the thermal behaviour of the drug-polymer dried gel samples. The melting peaks associated with both drugs, which were present in the thermograms of the drug-polymer physical mixtures, were not visible in the thermograms of the drug-polymer dried gel samples. This behaviour could be explained by the loss of drug crystallinity due to its interaction with the polymer. Moreover, such behaviour can be associated with the hindered swelling ability of Xanthan Gum tablets upon incorporation of either of the two drugs. This is due to the inability of Xanthan Gum to hydrate fully because of its interaction with the drugs.

However, the nature and properties of the gel layers formed on the surface of Xanthan Gum tablets containing the two drugs were significantly different. This was noticeable from the difference in the rheological behaviour of the Xanthan Gum gel systems containing the two drugs. Moreover, this difference in drug influence was also clear in the scanning electron microscopy images of the gel layers formed on the different tablets (Section 5.3.3.). Such variation in the drug influence was attributed to the different solubility of the two drugs with Orphenadrine HCl being more soluble. Moreover, the stronger acidic hydrochloride moiety in Orphenadrine HCl when compared to the citrate moiety in Orphenadrine Citrate could have played an additional role in hindering the hydration of Xanthan Gum. This was indicated by the increased inhibitory influence of Orphenadrine HCl on Xanthan Gum rheological properties with increased gel concentration.

The results of the qualitative investigations of Xanthan Gum gels (Chapter 6) clarified some of the characteristics associated with the hydration patterns of round and elongated Xanthan Gum tablets (Chapter 5). The occurrence and later disappearance of cracks within the structure of the tablets during the hydration process was only noted in tablets containing the drug Orphenadrine HCl. This pattern was clearly mirrored in the rheological properties of the gels containing such drug. Moreover, the magnitude of crack formation was more profound in tablets with higher degrees of face curvature. This indicated a correlation between the influence of tablet and formulation variables on the hydration behaviour of this type of hydrophilic matrix tablets. It could thus be concluded that drug solubility and salt form become of special importance during the design of hydrophilic matrix tablets with potentially interacting polymer and drug. Moreover, the choice of the degree of tablet face curvature should be given special attention as tablets with deeper curvatures could undergo undesirable behavioural patterns and loss of structural integrity.

The results of tablet dissolution studies (Chapter 7) indicated a trend consistent with the hydration behaviour of the tablets where the degree of tablet face curvature was the main significant factor influencing the dissolution characteristics of both drugs and polymer. The effect of tablet overall porosity on tablet dissolution characteristics was less evident. Thus the degree of tablet face curvature could be considered the main dosage form related driving force for tablet dissolution.

As a general conclusion, it could be stated that the degree of tablet face curvature, the overall porosity of the tablet, and the nature of the formulation used in tablet production including the solubility of the used drug, are all important and correlated factors that should be taken into account during the design and formulation of pharmaceutical tablets based on the hydrophilic matrix technology. The influence of these factors on tablet properties varies in magnitude. However, they all have a potential to influence the formulation, manufacturing, handling and subsequently behaviour of hydrophilic matrix tablets.

A further outcome of this study is the understanding of the strengths and limitations of statistical analysis techniques in the investigation, comparison, and presentation of the in-vitro behavioural characteristics associated with hydrophilic matrix tablets. The use of analysis of variance (ANOVA) provided a comprehensive method for the investigation of the tensile strength values associated with round and elongated hydrophilic matrix tablets with the added ability to identify cases of significant differences between the tensile strength values of the different tablets.

In terms of tablet swelling and dissolution profiles, the use of ANOVA provided an intensive technique of investigating the different stages of tablet hydration. The use of multivariate analysis of variance (MANOVA) presented a desirable method for investigating the entire tablet swelling and dissolution process, providing the ability to compare the overall

swelling and dissolution processes associated with tablets of different face curvatures and porosities.

It could thus be concluded that the use of statistical analysis techniques provided a convenient and informative method in the investigation of the in-vitro behaviour of hydrophilic matrix tablets.

8.2. Future work:

One possible option for future work could be the investigation of the influence of varying the nature of the formulations used in tablet production, mainly the size parameters of the formulation ingredients. Changing the particle size of either the polymer or drug, or both of them, could have a significant influence on the compaction properties of the powder mixtures and thus lead to variations in the internal structural properties of the produced tablets, and thus their physical and hydration properties. Moreover, the dissolution and hydration properties of the drug and polymer would be significantly influenced by the change in their particle size. This becomes particularly important with formulations similar to the ones used in this study, in which there is a potential for an ionic interaction between the two entities.

Another possibility for further investigation is associated with the properties of the gel layers produced by such formulations upon hydration. The in vitro behaviour of flat and curved-face hydrophilic matrix

tablets formulated using other ionic polymers, excipients, and drugs with different physico-chemical properties could be undertaken, by exploring the relationships between the rheological properties of the gel layers formed on the surface of such tablets and the in vitro behaviour of the tablets, for example, swelling and dissolution.

In terms of variables associated with the nature of the dosage form, one potential future aim could be to investigate the influence of any concurrent change in tablet size and degree of tablet face curvature, i.e. to investigate the degrees of tablet face curvature used in this study in tablets with different height and diameter values. This would give further insight into the influence of tablet face curvature on the characteristics of tablets with different overall sizes, as the overall size of the tablets could have a clear influence on their structural and hydration patterns.

All the hydrophilic matrix tablets investigated in this study were produced by the process of direct compression of the different powder mixtures. This method is widely used in tablet production. However, other techniques have also been employed in the production of hydrophilic matrix tablets to manipulate their physical and dissolution properties. Some of these methods include the production of layered tablets. Such tablets comprise of multiple layers which are formulated using different materials, and pressed together into one tablet to provide particular dissolution characteristics or pulsatile drug release (Conte et al 1993, Qiu et al 1998, Sungthongjeen et al 2004, Shajan and Poddar 2004). The

presence of multiple layers within the tablet may influence its structural properties. It is thus a potential future investigation to study the influence of tablet face curvature and formulation properties on the hydration and dissolution patterns of layered tablets.

Another possibility for future work exists in exploring the nature and development of structural changes occurring within the hydrating tablets, using non-destructive methods. Such investigation would provide further understanding of the occurrence and propagation of cracks within tablets containing the drug Orphenadrine HCl. Furthermore, it would help in investigating the possible existence of such cracks in the other tablets. The investigative use of such techniques was initiated using ultrasound imaging. Preliminary ultrasound imaging studies were conducted on round convex tablets produced using the three different formulations, before and during tablet hydration. However, the specifications of the imaging system available did not facilitate the attainment of images with sufficient resolution to point out any specific differences between the different tablets. Thus one potential possibility for future work is the investigation of the hydration of the tablets using an ultrasound imaging system with higher resolution power to get more insight into the internal structural changes occurring within the hydrating tablets.

Other imaging techniques, which are non destructive in general and require minimal sample preparation and manipulation, have been introduced into literature for the investigation of the structural properties

of tablets in their solid state, including x-ray microtomography (Sinka et al 2004), and terahertz imaging (Ho et al 2007). It would thus be a possibility to study the potential use of such techniques in the investigation of hydrophilic matrix tablets prior and during their in-vitro hydration to correlate the external structural changes with any possible changes occurring within the internal structure of the tablets. Such techniques, as well as ultrasound imaging, would present a particular advantage in the investigation of hydrophilic matrix tablets in which ionic interactions take place upon tablet hydration, due to the fact that no colouring or contrast agent is usually needed in their use.

The aim of this work was to investigate the influence of factors associated with the shape, structure and formulation of hydrophilic matrix tablets on the in vitro performance of such tablets. This focused nature of the study was chosen in order to present a clear picture about the influence of these factors without any complications or influences from external factors not directly related to the properties of the dosage form “tablet”. However, one other major influencing factor on the performance of hydrophilic matrix tablets is the surrounding hydration or dissolution medium, whether in terms of its physico-chemical properties or its hydrodynamics. Such variables could have a major influence on the hydration and erosion of the polymer incorporated into the formulation of hydrophilic matrix tablets, such as Xanthan Gum, in addition to their effect on drug solubility. They could thus affect the process of tablet hydration and drug release. It is thus a main option for future work to investigate

the same tablet properties and behaviours that were examined in this study but using different compositions and hydrodynamics of the hydration or dissolution medium surrounding the tablets.

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